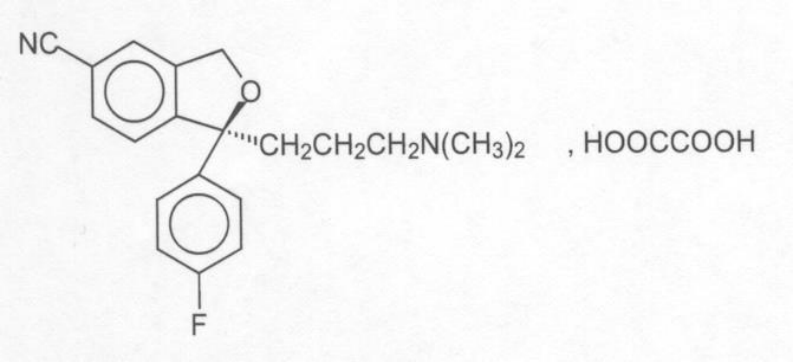
Loxalate

Escitalopram oxalate

NAME OF THE MEDICINE

Active ingredient	:	Escitalopram oxalate
Chemical name	:	S-(+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrogen oxalate.
Structural formula	:	

Molecular formula	:	$C_{20}H_{21}FN_2O.C_2H_2O_4$	Molecular weight	:	414.42
			CAS Registry no.	:	219861-08-2

DESCRIPTION

Escitalopram is the active enantiomer (*S*-enantiomer) of citalopram. Escitalopram oxalate is a fine white to yellow, crystalline material.

Escitalopram oxalate is sparingly soluble in water, slightly soluble in acetone, soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

Excipients in Loxalate: cellulose - microcrystalline, silica - colloidal anhydrous, talc -purified, croscarmellose sodium, magnesium stearate. The coating on each tablet, Opadry White OY-LS-28908 (ARTG No. 2596), contains lactose.

Loxalate 5 mg tablets are convex, white, film-coated tablets, marked with “EC/5” on one side and “G” on the other side.

Loxalate 10 mg tablets are convex, white, film-coated tablets, marked with “EC/10” on one side and “G” on the other side.

Loxalate 20 mg tablets are convex, white, film-coated tablets, marked with “EC/20” on one side and “G” on the other side.

PHARMACOLOGY

Pharmacodynamics

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT)-uptake *(in vitro* IC_{50} 2nM).

The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.

Escitalopram is a highly selective Serotonin Reuptake Inhibitor (SSRI). On the basis of *in vitro* studies, escitalopram had no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRIs, escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and DA D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity.

Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter.

Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing properties of the S-enantiomer in citalopram.

In healthy volunteers and in patients, escitalopram did not cause clinically significant changes in vital signs, ECGs, or laboratory parameters.

S-demethylcitalopram, the main plasma metabolite, attains about 30 % of parent compound levels after oral dosing and is about 5-fold less potent at inhibiting 5-HT reuptake than escitalopram *in vitro*. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 hours after multiple dosing). While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (about 80 %).

Distribution

The apparent volume of distribution ($V_{d,\beta}$/F) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55 %.

Metabolism

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Excretion

The elimination half-life ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. Approximately 8.0 % of escitalopram is eliminated unchanged in urine and 9.6 % as the S-demethylcitalopram metabolite based on 20 mg escitalopram data. Hepatic clearance is mainly by the P450 enzyme system.

The pharmacokinetics of escitalopram are linear over the clinical dosage range. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (Range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Reduced hepatic function

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Reduced renal function

While there is no specific data, the use of escitalopram in reduced renal function may be extrapolated from that of racemic citalopram. Escitalopram is expected to be eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Elderly patients (>65 years)

Escitalopram pharmacokinetics in subjects > 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50 % in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients.

Gender

In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, Cmax and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Polymorphism

It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

Loxalate should not be used in the treatment of major depression in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Two fixed dose studies and one flexible dose study has shown escitalopram in the dose range 10-20 mg/day to be more efficacious than placebo in the treatment of depression.

All three studies were randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. Two of the studies included an active reference (citalopram). All three studies consisted of a 1-week single-blind placebo lead-in period followed by an 8-week double-blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Asberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of 10 items that measure core symptoms of depression, such as sadness, tension, pessimism and suicidal thoughts. Each item is rated on a scale of 0 (no abnormality) to 6 (severe). The populations studied were therefore defined as suffering from moderate to severe depression (mean MADRS score 29). A total of 591 patients received escitalopram in these studies.

All three studies showed escitalopram to be statistically significantly superior to placebo on the ITT LOCF analysis of the mean change from baseline in the MADRS total score ($p \leq 0.01$). The magnitude of the difference between escitalopram and placebo in the MADRS change score ranged from 2.7 to 4.6 (mean of these values: 3.6). The magnitude of the difference for citalopram ranged from 1.5 to 2.5 (mean of these values: 2.0). The magnitude of the difference is larger with escitalopram than with citalopram.

Escitalopram demonstrated a significant early difference compared to placebo from week 2 onwards on the MADRS (week 1 in observed cases analysis). Likewise, the Clinical Global Impression - Improvement items (CGI-I) differed significantly from placebo from week 1 onwards. These early differences were not seen with racemic citalopram.

In the study with two parallel escitalopram dose groups, analysis of subgroups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D >25) receiving 20 mg/day as compared to 10 mg/day. The Hamilton Rating Scale for Depression (HAM-D) consists of 17 to 24 items reflecting core symptoms of depression. Each item is scored on a 3, 4, or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

In a fourth flexible-dose study with a similar design, the primary analysis did not distinguish a significant drug/placebo difference for either escitalopram or citalopram over 8 weeks on the MADRS change score in the LOCF dataset. However, on the basis of the OC analysis, both escitalopram and citalopram were significantly better than placebo ($p \leq 0.05$; difference between escitalopram and placebo: 2.9).

Escitalopram demonstrated efficacy in the treatment of anxiety symptoms associated with depression. In the three positive double-blind placebo-controlled studies escitalopram was shown to be effective compared to placebo on the MADRS anxiety items; inner tension and sleep disturbances. Furthermore, in the one study where the Hamilton Anxiety Scale (HAM-A) and the anxiety factor of the Hamilton Depression Rating Scale (HAM-D scale) were used, results have shown that escitalopram was significantly better than placebo.

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open label treatment phase with escitalopram 10 or 20 mg/day, were randomised to continuation of escitalopram at the same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open label phase was defined as a decrease of the MADRS total score to ≤ 12.

Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo (26 % vs. 40 %; hazard ratio = 0.56, p = 0.013).

Further evidence of long-term efficacy is provided in a 6-month study which compared escitalopram 10 mg/day to citalopram 20 mg/day over a 6-month treatment period. Analysis of the primary endpoint (the development of the MADRS total scores over 24 weeks) demonstrated escitalopram to be at least as efficacious as citalopram in the long-term treatment of depression. Secondary analyses showed that, while both treatments resulted in numerical improvements in ratings in the MADRS, HAM-A and the CGI, escitalopram was statistically superior to citalopram in several analyses, both during and at the end of the study.

Additional supportive evidence of the sustained efficacy of escitalopram treatment is demonstrated in an open-label 12-month study. The efficacy of escitalopram was maintained throughout the study, as measured by MADRS total score and CGI-S score. Patients showed continued improvement, with total MADRS scores falling from 14.2 at baseline to 5.8 at last assessment, and CGI-scores falling from 2.7 at baseline to 1.6 at last assessment.

A study in the elderly did not provide conclusive efficacy results for escitalopram, as the reference drug (fluoxetine) failed to differentiate from placebo. However, safety data from this study showed escitalopram to be well tolerated.

INDICATIONS

Treatment of major depression.

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in Loxalate (see **DESCRIPTION**).

Monoamine Oxidase Inhibitors – Escitalopram should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI, and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. Similarly, at least 14 days should be allowed after stopping escitalopram before starting a MAOI or RIMA. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see PRECAUTIONS – **INTERACTIONS WITH OTHER MEDICINES**).

Pimozide – Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS – **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Clinical worsening and suicide risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms are present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16 week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those

receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4 %, compared with 2 % of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Loxalate should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Haemorrhage

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). Loxalate should therefore be used with caution in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Hyponatraemia

Probably due to inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia has been reported as a rare adverse reaction with the use of SSRIs. Especially elderly patients seem to be a risk group.

Seizures

The drug should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency (see **PRECAUTIONS – Preclinical Safety**).

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Mania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

ECT (electroconvulsive therapy)

There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

Effects on ability to drive and use machines

Escitalopram does not impair intellectual function and psychomotor performance. However, as with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

Discontinuation

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.

The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 - 3 months or more). It is therefore advised that escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see **DOSAGE AND ADMINISTRATION**).

Cardiac disease

Escitalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, escitalopram causes a small decrease in heart rate. Consequently, caution should be observed when escitalopram is initiated in patients with pre-existing slow heart rate.

Impaired hepatic function

In subjects with hepatic impairment, clearance of escitalopram was decreased and plasma concentrations were increased. The dose of escitalopram in hepatically impaired patients should therefore be reduced (see **PHARMACOLOGY – Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

Impaired renal function

Escitalopram is extensively metabolised and excretion of unchanged drug in urine is a minor route of elimination. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) and escitalopram should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**).

Preclinical Safety

High doses of escitalopram, which resulted in plasma C_{max}, for escitalopram and metabolites at least 8-fold greater than anticipated clinically, have been associated with convulsions, ECG abnormalities and cardiovascular changes in experimental animals. Of the cardiovascular changes, cardiotoxicity (including congestive heart failure) was observed in comparative toxicological studies in rats following oral escitalopram or citalopram administration for 4 to 13 weeks and appears to correlate with peak plasma concentrations although its exact mechanism is not clear. Clinical experience with citalopram, and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Effects on Fertility

No fertility studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Animal data have shown that some SSRIs induce a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm. No animal data related to this aspect are available for escitalopram.

Animal data have shown that some SSRIs may affect sperm quality.

Use in Pregnancy (Category C)

No relevant epidemiological data or well-controlled studies in pregnant women are available for escitalopram. SSRIs have had limited use in pregnancy without a reported increase in birth defects.

Neonates should be observed if maternal use of Loxalate continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy. If escitalopram is used until or shortly before birth, discontinuation effects in the newborn are possible.

Neonates exposed to Loxalate, other SSRIs (Selective Serotonin Reuptake Inhibitors), or SNRIs (Serotonin Norepinephrine Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In the majority of cases the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological studies have shown that the use of SSRI's (including escitalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased post-implantation loss and reduced fetal weight at systemic exposure levels (based on AUC) ca. 11-fold that anticipated clinically, with no effects seen at 6-fold. No teratogenicity was evident in this study at relative systemic exposure levels of ca. 15 (based on AUC).

There were no peri/postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) ca. 2-fold that anticipated clinically. However, the number of stillbirths was increased and the size, weight and postnatal survival of offspring was decreased at a relative systemic exposure level ca.5.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit.

Use in Lactation

It is expected that escitalopram, like citalopram, will be excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4-5.1 % (below the notional 10 % level of concern).

Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use of escitalopram in breastfeeding women, the decision to breast feed should always be made as an individual risk/benefit analysis.

Paediatric use (children and adolescents < 18 years)

The efficacy and safety of escitalopram has not been established in children and adolescents less than 18 years of age. Consequently, escitalopram should not be used in children and adolescents less than 18 years of age.

Use in the elderly (> 65 years)

Escitalopram AUC and half-life were increased in subjects ≥ 65 years of age compared to younger subjects in a single-dose and a multiple-dose pharmacokinetic study. The dose of escitalopram in elderly patients should therefore be reduced (see **DOSAGE AND ADMINISTRATION**).

Carcinogenicity

No carcinogenicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

Citalopram did not show any carcinogenic activity in long-term oral studies using mice and rats at doses up to 240 and 80 mg/kg/day, respectively.

Genotoxicity

No genotoxicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

INTERACTIONS WITH OTHER MEDICINES

MAOIs

Co-administration with MAO inhibitors may cause serotonin syndrome (see **CONTRAINDICATIONS**).

Serotonin syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (Hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with escitalopram should be discontinued if such events occur and supportive symptomatic treatment initiated.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction with citalopram noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see **CONTRAINDICATIONS**).

Serotonergic drugs

Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, Hypericum perforatum (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and tryptophan

There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Medicines affecting the central nervous system

Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines lowering the seizure threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol).

Hepatic enzymes

Escitalopram has a low potential for clinically significant drug interactions. In vitro studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A4, and a weak inhibitor of 2D6.

Effects of other drugs on escitalopram in vivo

The pharmacokinetics of escitalopram was not changed by co-administration with ritonavir (CYP3A4 inhibitor). Furthermore co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Co-administration of escitalopram with omeprazole (a CYP2C19 inhibitor) resulted in a moderate (approximately 50%) increase in plasma concentrations of escitalopram and a small but statistically significant increase (31%) in the terminal half-life of escitalopram (see also Poor metabolisers of CYP2C19 under **DOSAGE AND ADMINISTRATION**).

Co-administration of escitalopram with cimetidine (moderately potent general enzyme inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluoxetine, fluvoxamine, lansoprazole, and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement (see also Poor metabolisers of CYP2C19 under **DOSAGE AND ADMINISTRATION**).

Effects of escitalopram on other drugs in vivo

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortryptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with metoprolol (a CYP2D6 substrate) resulted in a twofold increase in the plasma levels of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with escitalopram.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin, etc)

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with Loxalate.

Alcohol

The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse reactions observed with escitalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually decrease in intensity and frequency with continued treatment and generally do not lead to a cessation of therapy. Data from short-term placebo controlled studies are presented below. The safety data from the long-term studies showed a similar profile.

TreatmentEmergent Adverse Events with an Incidence of ≥ 1 % in placebo-controlled trials

Figures marked with * in below table indicate adverse reactions (incidence with escitalopram statistically significantly different from placebo (P< 0.05).

System Organ Class & Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
Patients Treated	1795	2632
Patients with Treatment Emergent Adverse Event	1135 (63.2)	1891 (71.8)
GASTROINTESTINAL SYSTEM DISORDERS		
nausea	151 (8.4)	481 (18.3)*
diarrhoea	91 (5.1)	207 (7.9)*

mouth dry	74 (4.1)	152 (5.8)*
constipation	42 (2.3)	71 (2.7)
abdominal pain	47 (2.6)	68 (2.6)
vomiting	29 (1.6)	54 (2.1)
dyspepsia	30 (1.7)	33 (1.3)
flatulence	15 (0.8)	31 (1.2)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
headache	305 (17.0)	506 (19.2)
dizziness	64 (3.6)	147 (5.6)*
paraesthesia	13 (0.7)	35 (1.3)
migraine	17 (0.9)	23 (0.8)
tremor	15 (0.8)	33 (1.3)
PSYCHIATRIC DISORDERS		
insomnia	82 (4.6)	245 (9.3)*
somnolence	62 (3.5)	217 (8.2)*
anorexia	12 (0.7)	56 (2.1)*
libido decreased	21 (1.2)	102 (3.9)*
anxiety	44 (2.5)	77 (2.9)
appetite decreased	8 (0.5)	35 (1.3)*
agitation	6 (0.3)	33 (1.3)*
nervousness	13 (0.7)	25 (1.0)
dreaming abnormal	18 (1.0)	41 (1.6)
impotence [gs]	4 (0.6)	22 (2.2)*
RESPIRATORY SYSTEM DISORDERS		
upper respiratory tract infection	91 (5.1)	96 (3.6)
coughing	18 (1.1)	24 (0.9)
rhinitis	81 (4.8)	146 (5.5)
sinusitis	24 (1.3)	46 (1.7)
pharyngitis	44 (2.5)	57 (2.2)
yawning	3 (0.2)	58 (2.2)*
bronchitis	31 (1.7)*	26 (0.9)
BODY AS A WHOLE - GENERAL DISORDERS		
influenza-like symptoms	65 (3.6)	87 (3.3)
fatigue	62 (3.5)	230 (8.7)*
back pain	61 (3.4)	74 (2.8)
SKIN AND APPENDAGES DISORDERS		
sweating increased	27 (1.5)	145 (5.5)*
MUSCULOSKELETAL SYSTEM DISORDERS		
arthralgia	22 (1.2)	27 (1.0)
REPRODUCTIVE DISORDERS, FEMALE		
anorgasmia [gs]	3 (0.3)	47 (2.9)*
METABOLIC AND NUTRITIONAL DISORDERS		
weight increase	20 (1.1)	45 (1.7)
REPRODUCTIVE DISORDERS, MALE		
ejaculation disorder [gs]	3 (0.5)	48 (4.7)*
ejaculation failure [gs]	1 (0.2)	27 (2.7)*
CARDIOVASCULAR DISORDERS		
hypertension	24 (1.3)*	13 (0.5)
HEART RATE AND RHYTHM DISORDERS		
palpitation	15 (0.8)	30 (1.1)
SECONDARY TERMS		
inflicted injury (unintended injury)	22 (1.2)	23 (0.8)

* = Statistically significant difference escitalopram vs placebo (P< 0.05)
[gs) = gender specific

Adverse Events in Relation to Dose

The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5 % in either the 10 mg or 20 mg escitalopram groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials. The overall incidence rates of adverse events in 10 mg escitalopram treated patients (66 %) was similar to that of the placebo treated patients (61 %), while the incidence rate in 20 mg/day escitalopram

treated patients was greater (86 %). Common adverse events that occurred in the 20 mg/day escitalopram group with an incidence approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group are shown below.

Incidence of common adverse events* in patients with major depression receiving placebo, 10 mg/day escitalopram or 20 mg/day escitalopram			
Adverse Event	**Placebo (N=311)**	**10 mg/day escitalopram (N=310)**	**20 mg/day escitalopram (N=125)**
Insomnia	4 %	7 %	14 %
Diarrhoea	5 %	6 %	14 %
Dry mouth	3 %	4 %	9 %
Somnolence	1 %	4 %	9 %
Dizziness	2 %	4 %	7 %
Sweating increased	< 1 %	3 %	8 %
Constipation	1 %	3 %	6 %
Fatigue	2 %	2 %	6 %
Indigestion	1 %	2 %	6 %
*adverse events with an incidence rate of at least 5 % in either escitalopram groups and with an incidence rate in the 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group.			

Vital Sign Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment.

ECG Changes

Cases of QT prolongation have been reported during the post-marketing period with both citalopram and escitalopram. Citalopram can cause dose-dependent QT interval prolongation. In an ECG study, the observed change from baseline QTc (Fridericia correction) was 7.5 msec at the 20 mg/day dose and 16.7 msec at the 60 mg/day dose of citalopram. The effect of escitalopram on the QT interval was similarly studied at doses of 10 mg/day and 30 mg/day. The change from baseline QTc (Fridericia correction) was 4.3 msec at the 10 mg/day dose and 10.7 msec with the above recommended dose of 30 mg/day. The QTc interval prolongation observed with 60 mg citalopram exceeded that observed with 30 mg escitalopram. It is probable that the R-enantiomer and its metabolites in racemic citalopram contribute to these effects.

Weight Changes

Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

In clinical studies there were no signals of clinically important changes in either various serum chemistry, haematology, and urinalysis parameters associated with escitalopram treatment compared to placebo or in the incidence of patients meeting the criteria for potentially clinically significant changes from baseline in these variables.

For abnormal laboratory changes registered as either uncommon events or serious adverse events from ongoing trials and observed during (but not necessarily caused by) treatment with escitalopram, please see Other Events Observed during the Premarketing Evaluation of escitalopram.

Other Events Observed during the Premarketing Evaluation of escitalopram

Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1 % and serious adverse events from ongoing trials. All reported events are included except those already listed in the table or

elsewhere in the Adverse Effects section, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with escitalopram, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients.

Application Site Disorders

Uncommon: otitis externa, cellulitis.

Body as a whole

Uncommon: allergy, aggravated allergy, allergic reactions, asthenia, carpal tunnel syndrome, chest pain, chest tightness, fever, hernia, leg pain, limb pain, neck pain, oedema, oedema of extremities, peripheral oedema, rigors, malaise, syncope, scar..

Cardiovascular Disorders, General

Uncommon: hypertension aggravated, hypotension, hypertension, abnormal ECG.

Central and Peripheral Nervous System Disorders

Uncommon: ataxia, dysaesthesia, dysequilibrium, dysgeusia, dystonia, hyperkinesia, hyperreflexia, hypertonia, hypoaesthesia, leg cramps, lightheadedness, muscle contractions, nerve root lesion, neuralgia, neuropathy, paralysis, sedation, tetany, tics, twitching, vertigo.

Gastrointestinal System Disorders

Uncommon: abdominal cramp, abdominal discomfort, belching, bloating, change in bowel habit, colitis, colitis ulcerative, enteritis, epigastric discomfort, gastritis, gastroesophageal reflux, haemorrhoids, heartburn, increased stool frequency, irritable bowel syndrome, melaena, periodontal destruction, rectal haemorrhage, tooth disorder, toothache, ulcerative stomatitis.

Hearing and Vestibular Disorders

Uncommon: deafness, earache, tinnitus, otosalpingitis, ear disorder.

Heart Rate and Rhythm Disorders

Uncommon: bradycardia, tachycardia.

Liver and Biliary System Disorders

Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and Nutritional Disorders

Uncommon: diabetes mellitus, hyperglycaemia, weight decrease, abnormal glucose tolerance, hyperlipaemia, xerophthalmia, gout, thirst, hypercholesterolaemia.

Musculoskeletal System Disorders

Uncommon: arthritis, arthropathy, arthrosis, bursitis, costochondritis, fascitis plantar, fibromyalgia, ischial neuralgia, jaw stiffness, muscle cramp, muscle spasms, muscle stiffness, muscle tightness, muscle weakness, myalgia, myopathy, osteoporosis, pain neck/shoulder, tendinitis, tenosynovitis.

Myo-, Endo- and Pericardial & valve disorders

Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm

Uncommon: ovarian cyst, uterine fibroid, female breast neoplasm.

Platelet, Bleeding & Clotting disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Poison Specific Terms

Uncommon: sting.

Psychiatric Disorders

Uncommon: aggressive reaction, amnesia, apathy, bruxism, carbohydrate craving, concentration impairment, confusion, depersonalisation, depression, depression aggravated, emotional lability, excitability, feeling unreal, forgetfulness, hallucination, hypomania, increased appetite, irritability, jitteriness, lethargy, loss of libido, obsessive-compulsive disorder, panic reaction, paroniria, restlessness aggravated, sleep disorder, snoring, suicide attempt, thinking abnormal.

Red Blood Cell Disorders

Uncommon: anaemia hypochromic, anaemia.

Reproductive disorders / female

Uncommon: amenorrhoea, atrophic vaginitis, breast pain, genital infection, intermenstrual bleeding, menopausal symptoms, menorrhagia, menstrual cramps, menstrual disorder, premenstrual tension, postmenopausal bleeding, sexual function abnormality, unintended pregnancy, dysmenorrhoea, vaginal haemorrhage, vaginal candidiasis, vaginitis.

Reproductive disorders / male

Uncommon: ejaculation delayed, prostatic disorder.

Resistance Mechanism Disorders

Uncommon: moniliasis genital, abscess, infection, herpes simplex, herpes zoster, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis.

Respiratory System Disorders

Uncommon: asthma, dyspnoea, laryngitis, nasal congestion, nasopharyngitis, pneumonia, respiratory tract infection, shortness of breath, sinus congestion, sinus headache, sleep apnoea, tracheitis, throat tightness.

Skin and Appendages Disorders

Uncommon: acne, alopecia, dermatitis, dermatitis fungal, dermatitis lichenoid, dry skin, eczema, erythematous rash, furunculosis, onychomycosis, pruritus, psoriasis aggravated, rash, rash pustular, skin disorder, urticaria, verruca.

Secondary Terms

Uncommon: accidental injury, bite, burn, fall, fractured neck of femur, alcohol problem, traumatic haematoma, cyst, food poisoning, lumbar disc lesion, surgical intervention.

Special Senses Other, Disorders

Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS, vision blurred.

Urinary System Disorders

Uncommon: cystitis, dysuria, facial oedema, micturition frequency, micturition disorder, nocturia, polyuria, pyelonephritis, renal calculus, urinary frequency, urinary incontinence, urinary tract infection.

Vascular (Extracardiac) Disorders

Uncommon: flushing, cerebrovascular disorder, hot flushes [gs], ocular haemorrhage, peripheral ischaemia, vein disorder, varicose vein, vein distended.

Vision Disorders

Uncommon: accommodation abnormal, blepharospasm, mydriasis, eye pain, eye infection, vision abnormal, vision blurred, visual disturbance.

White Cell and Reticuloendothelial System Disorder

Uncommon: leucopenia.

In addition the following adverse reactions have been reported with racemic citalopram (all of which have also been reported for other SSRIs):

Disorders of metabolism and nutrition

Hyponatraemia, inappropriate ADH secretion (both especially in elderly women).

Neurological disorders

Convulsions, convulsions grand mal and extrapyramidal disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and incoordination).

Skin disorders

Ecchymoses, angioedema.

Furthermore a number of adverse reactions have been listed for other SSRIs. Although these are not listed as adverse reactions for escitalopram or citalopram, it cannot be excluded that these adverse reactions may occur with escitalopram. These SSRI class reactions are listed below:

Cardiovascular disorders

Postural hypotension

Hepatobiliary disorders

Abnormal liver function tests

Neurological disorders

Movement disorders.

Psychiatric disorders

Mania, panic attacks.

Renal and Urinary Disorders

Urinary retention

Reproductive disorders

Galactorrhoea.

Other Events Observed During the Postmarketing Evaluation of Escitalopram

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported in association with escitalopram treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the Adverse Effects section:

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental overdose, injury NOS , psychotic disorder.

In addition, although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment subsequent to the marketing of racemic citalopram and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, anaphylaxis, choreoathetosis, delirium, dyskinesia, epidermal necrolysis, erythema multiforme, gastrointestinal haemorrhage, haemolytic anaemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinaemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

Class effect

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

DOSAGE AND ADMINISTRATION

Adults

Escitalopram should be administered as a single oral dose of 10 mg once daily with or without food. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.Usually 2-4 weeks are necessary for antidepressant response, although the onset of therapeutic effect may be seen earlier. The treatment of a single episode of depression requires treatment over the acute and the medium term. After the symptoms resolve during acute treatment, a period of consolidation of the response is required. Therefore, treatment of a depressive episode should be continued for a minimum of 6 months.

When stopping SSRI therapy gradual dose reduction should be considered. Elderly patients (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg is the recommended maximum maintenance dose in the elderly (see **PHARMACOLOGY – Pharmacokinetics** and **PRECAUTIONS**).

Children and Adolescents (< 18 years of age)

Safety and efficacy have not been established in this population. Escitalopram should not be used in children and adolescents under 18 years of age (see **PRECAUTIONS**).

Reduced renal function

Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) (see **PRECAUTIONS**).

Reduced hepatic function

An initial dose of 5 mg daily for the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (see **PRECAUTIONS**).

Poor metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (see **PHARMACOLOGY – Pharmacokinetics** and **PRECAUTIONS – Interactions with Other Medicines**).

Discontinuation

Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over a period of at least one to two weeks is recommended. If unacceptable discontinuation symptoms occur following a decrease in the dose or upon discontinuation of treatment then resuming the previously prescribed dose may be considered. Subsequently, the dose may be decreased but at a more gradual rate.

OVERDOSAGE

In general, the main therapy for all overdoses is supportive and symptomatic care.

Toxicity

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Doses between 400 and 800 mg of escitalopram alone have been taken without any severe symptoms. No fatalities or sequelae were reported in the few cases with a higher dose (one patient survived ingestion of either 2,400 or 4,800 mg).

Symptoms

Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting), the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation)), and electrolyte/fluid balance conditions.

Treatment

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

In cases of overdosage it is advisable to contact the Poisons Information Center on 131126.

PRESENTATION AND STORAGE CONDITIONS

Loxalate Tablets 5 mg* (escitalopram oxalate equivalent to 5 mg of escitalopram)	:	5.5 mm normal convex white film coated tablet debossed "EC" over 5 on one side and "G" on the other, supplied in PVC/PVD C/Al blister packs or HDPE bottles of 28 and 30 tablets.
Loxalate Tablets 10 mg (escitalopram oxalate equivalent to 10 mg of escitalopram)	:	9.5 mm x 5.5 mm oblong normal convex white film coated tablet debossed "EC|10" on one side and "G" on the other, supplied in PVC/PVD C/Al blister packs or HDPE bottles* of 28 and 30* tablets.
Loxalate Tablets 20 mg (escitalopram oxalate equivalent to 20 mg of escitalopram)		12.5 mm x 7 mm oblong normal convex white film coated tablet debossed "EC|20" on one side and "G" on the other, supplied in PVC/PVD C/Al blister packs or HDPE bottles* of 28 and 30* tablets.

* Not marketed in Australia.

Store below 25 ºC. Protect from moisture

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.mylan.com.au

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

16 May 2008.

DATE OF MOST RECENT AMENDMENT

23 December 2016

Loxalate_pi\Dec16/02

Loxalate

contains the active ingredient escitalopram oxalate

CONSUMER MEDICINE INFORMATION

What is in this leaflet

This leaflet answers some common questions about Loxalate.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. Your doctor has weighed the risks of you taking Loxalate against the benefits expected for you.

If you have any concerns about taking this medicine, talk to your doctor or pharmacist.

Keep this leaflet with your medicine.

You may need to read it again.

What Loxalate is used for

Loxalate is used to treat depression.

Loxalate belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). Depression is longer lasting and/or more severe than the "low moods" everyone has from time to time due to the stress of everyday life. It is thought to be caused by a chemical imbalance in parts of the brain. This imbalance affects your whole body and can cause emotional and physical symptoms such as feeling low in spirit, loss of interest in activities, being unable to enjoy life, poor appetite or overeating, disturbed sleep, often waking up early, loss of sex drive, lack of energy and feeling guilty over nothing.

Loxalate corrects this chemical imbalance and may help relieve the symptoms of depression.

Ask your doctor if you have any questions about why Loxalate has been prescribed for you.

Your doctor may have prescribed Loxalate for another reason.

Loxalate is available only with a doctor's prescription.

Before you take Loxalate

When you must not take it

Do not take Loxalate if you are allergic to medicines containing citalopram or any of the ingredients listed at the end of this leaflet.

If you have an allergic reaction you may get a skin rash, have difficulty in breathing, get symptoms of hayfever or feel faint.

Do not take Loxalate if you are currently taking another medicine for depression known as a monoamine oxidase inhibitor (MAOI) or have taken one within the last 14 days.

Taking Loxalate with a MAOI may cause a serious reaction with a sudden increase in body temperature, extremely high blood pressure and convulsions (fits).

MAOIs are medicines used to treat depression and Parkinson's disease.

Some examples of MAOIs include moclobemide (e.g. Aurorix), phenelzine (Nardil), tranylcypromine (Parnate), selegiline (e.g. Eldepryl).

Do not take Loxalate if you are taking pimozide, a medicine used to treat mental disorders.

Do not take Loxalate after the expiry date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

Before you start to take it

Tell your doctor if you are allergic to any other medicines, foods, dyes or preservatives.

Tell your doctor if you are pregnant or plan to become pregnant.

Your doctor will provide information to you regarding the use of Loxalate, during pregnancy. You should not stop taking your tablets until you have spoken to your doctor. Your doctor will discuss the possible risks and benefits of taking Loxalate during pregnancy.

The general condition of your newborn baby might be affected by medicines like Loxalate.

Tell your doctor if you are breastfeeding or wish to breastfeed.

Loxalate passes into breast milk. However, it is not known whether this may affect your baby. Your doctor will discuss the risks and benefits of taking Loxalate when breastfeeding.

Tell your doctor if you have or have had any of the following medical conditions:

* heart problems
* diabetes
* epilepsy
* liver problems
* kidney problems
* bipolar disorder (manic depression)
* bleeding disorders.

If you have not told your doctor about any of the above, tell them before you start taking Loxalate.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from a pharmacy, supermarket or health food shop.

Some medicines and Loxalate may interfere with each other. These include:

* bupropion, a medicine helping to treat nicotine dependence
* medicines used to treat reflux and ulcers, such as cimetidine, omeprazole, esomeprazole and lansoprazole
* medicines known to prolong bleeding, e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
* ticlopidine and warfarin, medicines used to prevent blood clots
* mefloquine, an anti-malaria medicine
* sumatriptan, used to treat migraines
* tramadol, used to relieve pain
* some heart medications, e.g. flecainide, propafenone, metoprolol
* tryptophan, an amino-acid
* lithium, used to treat mood swings and some types of depression
* medicines used to treat certain mental and emotional conditions, also called antipsychotics; e.g. risperidone, thioridazine and haloperidol
* tricyclic antidepressants, e.g. imipramine, desipramine
* St John's Wort (Hypericum perforatum), a herbal remedy
* other medicines for depression, anxiety, obsessive-compulsive disorder or pre-menstrual dysphoric disorder.

These medicines may be affected by Loxalate or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Some combinations of medicines may increase the risk of serious side effects and are potentially life threatening.

Your doctor and pharmacist have more information on medicines to be careful with or avoid while taking this medicine.

Use in children

Do not give Loxalate to children. Loxalate should not be given to children under 18 years of age as there is no specific information about such use. Always ask your doctor before giving medicines to children.

Use in elderly

Loxalate can be given to elderly patients with a reduced dose. The effects of Loxalate in elderly patients are similar to that in other patients.

How to take Loxalate

Follow all directions given to you by your doctor and pharmacist carefully.

They may differ from the information contained in this leaflet.

If you do not understand the instructions on the pack or bottle, ask your doctor or pharmacist for help.

How much to take

Your doctor will tell you how much Loxalate to take.

The usual dose is 10 mg per day. This may be increased by your doctor to 20 mg per day.

The recommended maximum dose in elderly patients is 10 mg per day.

It is recommended that patients with liver disease receive an initial dose of 5 mg daily for the first two weeks. This dose may be increased to 10 mg daily.

How to take it

Swallow the tablets with a full glass of water.

Do not chew the tablets.

Loxalate 10 mg and 20 mg tablets can be divided in half if advised by your doctor or pharmacist.

When to take it

Take Loxalate at about the same time each day.

Taking it at the same time each day will have the best effect. It will also help you to remember when to take it.

Loxalate can be taken with or without food, either in the morning or evening.

How long to take it for

Continue taking your medicine for as long as your doctor tells you.

The length of treatment with Loxalate will depend on how quickly your symptoms improve.

Most medicines of this type take time to work, so do not be discouraged if you do not feel better right away. The treatment of depression may take at least six months.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take the missed dose as soon as you remember, and then go back to taking your tablets as you would normally.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, ask your doctor or pharmacist.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at the nearest hospital, if you think you or anyone else may have taken too much Loxalate. Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

Symptoms of an overdose may include dizziness, low blood pressure, nausea (feeling sick), vomiting, agitation, tremor (shaking) and rarely convulsions and coma.

While you are taking Loxalate

Things you must do

If you are about to be started on any new medicine, remind your doctor or pharmacist that you are taking Loxalate.

Tell any other doctors, dentists and pharmacists who treat you that you are taking Loxalate.

Tell your doctor immediately if you have any suicidal thoughts or other mental/mood changes.

A worsening of depressive symptoms including thoughts of suicide or self-harm may occur during initial treatment (generally the first one to two months) or when the doctor changes your dose. These symptoms should be controlled when the full effect of Loxalate takes place.

Children, adolescents or young adults under 25 years of age are more likely to experience these effects during the first few months of treatment.

Patients and caregivers should be alert and monitor for these effects.

If you or someone you know is showing any of the following warning signs of suicide while taking Loxalate, contact your doctor or a mental health professional right away or go to the nearest hospital for treatment:

* worsening of symptoms
* thoughts or talk of death or suicide
* thoughts or talk of self-harm or harm to others
* any recent attempts of self-harm
* increase in aggressive behaviour, irritability, or any other unusual changes in behaviour or mood.

If you become pregnant while taking Loxalate, tell your doctor immediately.

Keep all your doctor's appointments so that your progress can be checked.

Things you must not do

Do not stop taking Loxalate, or change the dose, without checking with your doctor.

Do not let yourself run out of Loxalate over weekends or holidays.

If you stop Loxalate suddenly or reduce the dose too quickly, you may get unwanted side effects such as dizziness, nausea (feeling sick) and headache.

Your doctor will tell you how to gradually reduce the amount of Loxalate you are taking before stopping completely.

Do not take Loxalate to treat any other complaints unless your doctor tells you to.

Do not give Loxalate to anyone else, even if they have the same condition as you.

Things to be careful of

Be careful driving or operating machinery until you know how Loxalate affects you.

Loxalate may cause dizziness, visual disturbances or drowsiness in some people. If you experience any of these, do not drive, operate machinery or do anything else that could be dangerous.

Avoid alcohol while you are taking this medicine.

It is not advisable to drink alcohol while you are being treated for depression.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Loxalate.

Loxalate helps most people with depression, but it may have unwanted side effects in a few people.

All medicines have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

* sinusitis (clogged or running nose)
* decreased appetite
* dry mouth
* nausea (feeling sick)
* diarrhoea
* constipation
* difficulties falling asleep
* fatigue

* sleepiness or drowsiness, yawning
* increased sweating
* sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties getting orgasm)

Tell your doctor as soon as possible if you notice any of the following:

* dizziness
* dizziness when you stand up due to low blood pressure#
* decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused)#
* abnormal liver function test (increased amounts of liver enzymes in the blood)#
* confusion, panic attacks#, anxiety, nervousness, agitation
* difficulties urinating#
* unusual secretion of breast milk#
* increased tendency to develop bruises#
* rash, itching, patches of circumscribed swellings.

The above list includes serious side effects that may require medical attention.

If any of the following happen, tell your doctor immediately or go to Accident and Emergency at your nearest hospital.

* signs of an allergic reaction such as skin rash, itching or hives; swelling of the face, lips or tongue which may cause difficulty in swallowing or breathing; wheezing or shortness of breath
* high fever, agitation, confusion, trembling and abrupt contractions of muscles may be signs of a rare condition called serotonin syndrome#
* mania#
* hallucinations
* seizures, tremors, movement disorders (involuntary movements of the muscles)#

The above list includes very serious side effects. You may need urgent medical attention or hospitalisation.

#The side effects marked with a hash (#) are rare side effects that are known to occur with medicines that work in a similar way to Loxalate.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell.

Other side effects not listed above may also occur in some people.

There is no evidence that Loxalate is addictive; however, if you suddenly stop taking Loxalate, you may get side effects. Tell your doctor if you get any side effects after stopping Loxalate.

After taking Loxalate

Storage

Keep Loxalate where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Keep your tablets in the pack or bottle until it is time to take them.

If you take the tablets out of the pack or bottle they may not keep well.

Keep your tablets protected from moisture in a cool dry place, where the temperature stays below 25 degrees C.

Do not store Loxalate or any other medicine in the bathroom or near a sink. Do not leave Loxalate in the car or on window stills.

Heat and dampness can destroy some medicines.

Disposal

If your doctor tells you to stop taking this medicine or the expiry date has passed, ask your pharmacist what to do with any medicine that is left over.

Product description

What it looks like

Loxalate is available in 2 strengths:

Loxalate Tablets 10 mg:

9.5 mm x 5.5 mm oblong normal convex white film-coated tablet debossed "EC|10" on one side and "G" on the other, supplied in packs of 28 tablets.

Loxalate Tablets 20 mg:

12.5mm x 7 mm oblong normal convex white film-coated tablet debossed "EC|20" on one side and "G" on the other, supplied in packs of 28 tablets.

Ingredients

The active ingredient in Loxalate is escitalopram oxalate.

Loxalate tablets contain 10 mg or 20 mg of escitalopram (as escitalopram oxalate).

The tablets also contain the following inactive ingredients:

* microcrystalline cellulose
* silica - colloidal anhydrous
* talc -purified
* croscarmellose sodium
* magnesium stearate
* Opadry White OY-LS-28908 (ARTG No. 2596)

The coating on each tablet contains lactose.

The tablets are gluten free.

Manufacturer

Loxalate is made in Australia by:
Alphapharm Pty Limited
(ABN 93 002 359 739)
Chase Building 2
Wentworth Park Road
Glebe NSW 2037
Phone: (02) 9298 3999

www.alphapharm.com.au

Medical Information
Phone: 1800 028 365

Australian registration numbers:

* Loxalate 10 mg
  AUST R 119964 (blister pack)
* Loxalate 20 mg
  AUST R 119966 (blister pack)

This leaflet was prepared on
16 June 2009.

Loxalate

contains the active ingredient escitalopram oxalate

CONSUMER MEDICINE INFORMATION

What is in this leaflet

This leaflet answers some common questions about Loxalate.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have benefits and risks. Your doctor has weighed the risks of you taking Loxalate against the benefits expected for you.

If you have any concerns about taking this medicine, talk to your doctor or pharmacist.

Keep this leaflet with your medicine.

You may need to read it again.

What Loxalate is used for

Loxalate is used to treat depression.

Loxalate belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). Depression is longer lasting and/or more severe than the "low moods" everyone has from time to time due to the stress of everyday life. It is thought to be caused by a chemical imbalance in parts of the brain. This imbalance affects your whole body and can cause emotional and physical symptoms such as feeling low in spirit, loss of interest in activities, being unable to enjoy life, poor appetite or overeating, disturbed sleep, often waking up early, loss of sex drive, lack of energy and feeling guilty over nothing.

Loxalate corrects this chemical imbalance and may help relieve the symptoms of depression.

Ask your doctor if you have any questions about why Loxalate has been prescribed for you.

Your doctor may have prescribed Loxalate for another reason.

Loxalate is available only with a doctor's prescription.

Before you take Loxalate

When you must not take it

Do not take Loxalate if you are allergic to medicines containing citalopram or any of the ingredients listed at the end of this leaflet.

If you have an allergic reaction you may get a skin rash, have difficulty in breathing, get symptoms of hayfever or feel faint.

Do not take Loxalate if you are currently taking another medicine for depression known as a monoamine oxidase inhibitor (MAOI) or have taken one within the last 14 days.

Taking Loxalate with a MAOI may cause a serious reaction with a sudden increase in body temperature, extremely high blood pressure and convulsions (fits).

MAOIs are medicines used to treat depression and Parkinson's disease. Some examples of MAOIs include moclobemide (e.g. Aurorix), phenelzine (Nardil), tranylcypromine (Parnate), selegiline (e.g. Eldepryl).

Do not take Loxalate if you are taking pimozide, a medicine used to treat mental disorders.

Do not take Loxalate after the expiry date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

Before you start to take it

Tell your doctor if you are allergic to any other medicines, foods, dyes or preservatives.

Tell your doctor if you are pregnant or plan to become pregnant.

Your doctor will provide information to you regarding the use of Loxalate, during pregnancy. You should not stop taking your tablets until you have spoken to your doctor. Your doctor will discuss the possible risks and benefits of taking Loxalate during pregnancy.

The general condition of your newborn baby might be affected by medicines like Loxalate.

Tell your doctor if you are breastfeeding or wish to breastfeed.

Loxalate passes into breast milk. However, it is not known whether this may affect your baby. Your doctor will discuss the risks and benefits of taking Loxalate when breastfeeding.

Tell your doctor if you have or have had any of the following medical conditions:

- heart problems
- diabetes
- epilepsy

- liver problems
- kidney problems
- bipolar disorder (manic depression)
- bleeding disorders.

If you have not told your doctor about any of the above, tell them before you start taking Loxalate.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from a pharmacy, supermarket or health food shop.

Some medicines and Loxalate may interfere with each other. These include:

- bupropion, a medicine helping to treat nicotine dependence
- medicines used to treat reflux and ulcers, such as cimetidine, omeprazole, esomeprazole and lansoprazole
- medicines known to prolong bleeding, e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
- ticlopidine and warfarin, medicines used to prevent blood clots
- mefloquine, an anti-malaria medicine
- sumatriptan, used to treat migraines
- tramadol, used to relieve pain
- some heart medications, e.g. flecainide, propafenone, metoprolol
- tryptophan, an amino-acid
- lithium, used to treat mood swings and some types of depression
- medicines used to treat certain mental and emotional conditions, also called antipsychotics; e.g. risperidone, thioridazine and haloperidol
- medicines affecting nerves, also called neuroleptics e.g. prochlorperazine
- tricyclic antidepressants, e.g. imipramine, desipramine, clomipramine, nortryptyline
- St John's Wort (Hypericum perforatum), a herbal remedy
- other medicines for depression, anxiety, obsessive-compulsive disorder or pre-menstrual dysphoric disorder.

These medicines may be affected by Loxalate or may affect how well it works. You may need different amounts of your medicines, or you may need to take different medicines.

Some combinations of medicines may increase the risk of serious side effects and are potentially life threatening.

Your doctor and pharmacist have more information on medicines to be careful with or avoid while taking this medicine.

Use in children

Do not give Loxalate to children. Loxalate should not be given to children under 18 years of age as there is no specific information about such use. Always ask your doctor before giving medicines to children.

Use in elderly

Loxalate can be given to elderly patients with a reduced dose. The effects of Loxalate in elderly patients are similar to that in other patients.

How to take Loxalate

Follow all directions given to you by your doctor and pharmacist carefully.

They may differ from the information contained in this leaflet.

If you do not understand the instructions on the pack or bottle, ask your doctor or pharmacist for help.

How much to take

Your doctor will tell you how much Loxalate to take.

The usual dose is 10 mg per day. This may be increased by your doctor to 20 mg per day.

The recommended maximum dose in elderly patients is 10 mg per day.

It is recommended that patients with liver disease receive an initial dose of 5 mg daily for the first two weeks. This dose may be increased to 10 mg daily.

How to take it

Swallow the tablets with a full glass of water.

Do not chew the tablets.

Loxalate 10 mg and 20 mg tablets can be divided in half if advised by your doctor or pharmacist.

When to take it

Take Loxalate at about the same time each day.

Taking it at the same time each day will have the best effect. It will also help you to remember when to take it.

Loxalate can be taken with or without food, either in the morning or evening.

How long to take it for

Continue taking your medicine for as long as your doctor tells you.

The length of treatment with Loxalate will depend on how quickly your symptoms improve.

Most medicines of this type take time to work, so do not be discouraged if you do not feel better right away. The treatment of depression may take at least six months.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Otherwise, take the missed dose as soon as you remember, and then go back to taking your tablets as you would normally.

Do not take a double dose to make up for the dose you missed.

If you are not sure what to do, ask your doctor or pharmacist.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at the nearest hospital, if you think you or anyone else may have taken too much Loxalate. Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

Symptoms of an overdose may include dizziness, low blood pressure, nausea (feeling sick), vomiting, agitation, tremor (shaking) and rarely convulsions and coma.

While you are taking Loxalate

Things you must do

If you are about to be started on any new medicine, remind your doctor or pharmacist that you are taking Loxalate.

Tell any other doctors, dentists and pharmacists who treat you that you are taking Loxalate.

Tell your doctor immediately if you have any suicidal thoughts or other mental/mood changes.

A worsening of depressive symptoms including thoughts of suicide or self-harm may occur during initial treatment (generally the first one to two months) or when the doctor changes your dose. These symptoms should be controlled when the full effect of Loxalate takes place.

Children, adolescents or young adults under 25 years of age are more likely to experience these effects during the first few months of treatment.

Patients and caregivers should be alert and monitor for these effects.

If you or someone you know is showing any of the following warning signs of suicide while taking Loxalate, contact your doctor or a mental health professional right away or go to the nearest hospital for treatment:

- worsening of symptoms
- thoughts or talk of death or suicide
- thoughts or talk of self-harm or harm to others
- any recent attempts of self-harm
- increase in aggressive behaviour, irritability, or any other unusual changes in behaviour or mood.

If you become pregnant while taking Loxalate, tell your doctor immediately.

Keep all your doctor's appointments so that your progress can be checked.

Things you must not do

Do not stop taking Loxalate, or change the dose, without checking with your doctor.

Do not let yourself run out of Loxalate over weekends or holidays.

If you stop Loxalate suddenly or reduce the dose too quickly, you may get unwanted side effects such as dizziness, nausea (feeling sick) and headache.

Your doctor will tell you how to gradually reduce the amount of Loxalate you are taking before stopping completely.

Do not take Loxalate to treat any other complaints unless your doctor tells you to.

Do not give Loxalate to anyone else, even if they have the same condition as you.

Things to be careful of

Be careful driving or operating machinery until you know how Loxalate affects you.

Loxalate may cause dizziness, visual disturbances or drowsiness in some people. If you experience any of these, do not drive, operate machinery or do anything else that could be dangerous.

Avoid alcohol while you are taking this medicine.

It is not advisable to drink alcohol while you are being treated with Loxalate.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Loxalate.

Loxalate helps most people with depression, but it may have unwanted side effects in a few people.

All medicines have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- headache
- clogged or runny nose, sore throat
- flu-like symptoms
- decreased appetite
- dry mouth
- nausea (feeling sick), vomiting
- diarrhoea
- constipation
- abdominal pain, indigestion, flatulence

- back pain, joint pain
- difficulties falling asleep
- fatigue
- sleepiness or drowsiness, yawning
- increased sweating
- sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties getting orgasm)

Tell your doctor as soon as possible if you notice any of the following:

- dizziness
- dizziness when you stand up due to low blood pressure#
- decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused)#
- abnormal liver function test (increased amounts of liver enzymes in the blood)#
- confusion, panic attacks#, anxiety, nervousness, agitation, abnormal dreams
- difficulties urinating#
- unusual secretion of breast milk#
- increased tendency to develop bruises#
- rash, itching, patches of circumscribed swellings.
- dark stools with stomach pain
- changes in heart rate

The above list includes serious side effects that may require medical attention.

If any of the following happen, tell your doctor immediately or go to Accident and Emergency at your nearest hospital.

- signs of an allergic reaction such as skin rash, itching or hives; swelling of the face, lips or tongue which may cause difficulty in swallowing or breathing; wheezing or shortness of breath
- high fever, agitation, confusion, trembling and abrupt contractions of muscles may be signs of a rare condition called serotonin syndrome#
- mania#
- hallucinations
- seizures, tremors, movement disorders (involuntary movements of the muscles)#

The above list includes very serious side effects. You may need urgent medical attention or hospitalisation.

#The side effects marked with a hash (#) are rare side effects that are known to occur with medicines that work in a similar way to Loxalate.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell.

Other side effects not listed above may also occur in some people.

There is no evidence that Loxalate is addictive; however, if you suddenly stop taking Loxalate, you may get side effects. Tell your doctor if you get any side effects after stopping Loxalate.

After taking Loxalate

Storage

Keep Loxalate where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Keep your tablets in the pack or bottle until it is time to take them.

If you take the tablets out of the pack or bottle they may not keep well.

Keep your tablets protected from moisture in a cool dry place, where the temperature stays below 25 degrees C.

Do not store Loxalate or any other medicine in the bathroom or near a sink. Do not leave Loxalate in the car or on window stills.

Heat and dampness can destroy some medicines.

Disposal

If your doctor tells you to stop taking this medicine or the expiry date has passed, ask your pharmacist what to do with any medicine that is left over.

Product description

What it looks like

Loxalate is available in 2 strengths:

Loxalate Tablets 10 mg:

9.5 mm x 5.5 mm oblong normal convex white film-coated tablet debossed "EC|10" on one side and "G" on the other, supplied in packs of 28 tablets.

Loxalate Tablets 20 mg:

12.5mm x 7 mm oblong normal convex white film-coated tablet debossed "EC|20" on one side and "G" on the other, supplied in packs of 28 tablets.

Ingredients

The active ingredient in Loxalate is escitalopram oxalate.

Loxalate tablets contain 10 mg or 20 mg of escitalopram (as escitalopram oxalate).

The tablets also contain the following inactive ingredients:

- microcrystalline cellulose
- colloidal anhydrous silica
- purified talc
- croscarmellose sodium
- magnesium stearate
- Opadry White OY-LS-28908 (ARTG No. 2596)

The coating on each tablet contains lactose.

The tablets are gluten free.

Manufacturer

Loxalate is made in Australia by:

Alphapharm Pty Limited

(ABN 93 002 359 739)

Level 1, 30 The Bond
30 – 34 Hickson Road
Millers Point NSW 2000
www.mylan.com.au

Medical Information
Phone: 1800 028 365

Australian registration numbers:

- Loxalate 10 mg
  AUST R 119964 (blister pack)
- Loxalate 20 mg
  AUST R 119966 (blister pack)

This leaflet was revised in September 2018.

Loxalate_cmi\Sep18

PRODUCT INFORMATION

LEXAPRO® Film-Coated Tablets
LEXAPRO® Oral Solution

NAME OF THE MEDICINE

LEXAPRO Film-Coated Tablets escitalopram (as oxalate)
LEXAPRO Oral Solution escitalopram (as oxalate)

Chemical name:

S(+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrogen oxalate.

CAS number:

219861-08-2

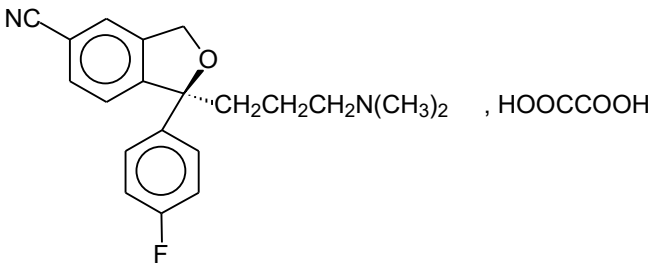
Molecular formula:

$C_{20}H_{21}FN_2O$, $C_2H_2O_4$

Molecular weight:

414.42

Structural formula:



DESCRIPTION

Escitalopram is the active enantiomer (S-enantiomer) of citalopram. Escitalopram oxalate is a fine white to yellow, crystalline material.

Escitalopram oxalate is sparingly soluble in water, slightly soluble in acetone, sparingly soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

LEXAPRO 10 mg tablets are oval, white, scored, film-coated tablets marked with "E" and "L" on one side.

LEXAPRO 20 mg tablets are oval, white, scored, film-coated tablets marked with "E" and "N" on one side.

LEXAPRO tablets contain the following excipients: microcrystalline cellulose, colloidal anhydrous silica, purified talc, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

LEXAPRO 20 mg/mL oral solution is a clear, nearly colourless to yellowish solution. It contains the following excipients: propyl gallate, anhydrous citric acid, ethanol, sodium hydroxide and purified water.

PHARMACOLOGY

Pharmacological actions

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT)-uptake (*in vitro* IC_{50} 2nM).

The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.

Escitalopram is a highly selective Serotonin Reuptake Inhibitor (SSRI). On the basis of in vitro studies, escitalopram had no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRIs, escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and DA D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity.

Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter.

Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the *R*-enantiomer is not inert but counteracts the serotonin-enhancing properties of the *S*-enantiomer in citalopram.

In healthy volunteers and in patients, escitalopram did not cause clinically significant changes in vital signs, ECGs, or laboratory parameters.

S-demethylcitalopram, the main plasma metabolite, attains about 30% of parent compound levels after oral dosing and is about 5-fold less potent at inhibiting 5-HT reuptake than

escitalopram in vitro. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 hours after multiple dosing). While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (about 80%).

Distribution

The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%.

Metabolism

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28 - 31% and < 5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Excretion

The elimination half-life ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. Approximately 8.0% of escitalopram is eliminated unchanged in urine and 9.6% as the S-demethylcitalopram metabolite based on 20 mg escitalopram data. Hepatic clearance is mainly by the P450 enzyme system.

The pharmacokinetics of escitalopram are linear over the clinical dosage range. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Special Populations

Reduced hepatic function

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Reduced renal function

While there is no specific data, the use of escitalopram in reduced renal function may be extrapolated from that of racemic citalopram. Escitalopram is expected to be eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Elderly patients (> 65 years)

Escitalopram pharmacokinetics in subjects > 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients.

Gender

In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Polymorphism

It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

LEXAPRO should not be used for the treatment of major depression, generalised anxiety disorder, social anxiety disorder and obsessive-compulsive disorder in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Major Depression

LEXAPRO should not be used in the treatment of children and adolescents under the age of 18 years.

Two fixed-dose studies and one flexible-dose study have shown escitalopram in the dose range 10 - 20 mg/day to be more efficacious than placebo in the treatment of depression. All three studies were randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. Two of the studies included an active reference (citalopram). All three studies consisted of a 1-week single-blind placebo lead-in period followed by an 8-week double-blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of 10 items that measure core symptoms of depression, such as sadness, tension, pessimism and suicidal thoughts. Each item is rated on a scale of 0 (no abnormality) to 6 (severe). The populations studied were therefore defined as suffering from moderate to severe depression (mean MADRS score 29). A total of 591 patients received escitalopram in these studies.

All three studies showed escitalopram to be statistically significantly superior to placebo on the ITT LOCF analysis of the mean change from baseline in the MADRS total score ($p \leq 0.01$). The magnitude of the difference between escitalopram and placebo in the MADRS change score ranged from 2.7 to 4.6 (mean of these values: 3.6). The magnitude of the difference for citalopram ranged from 1.5 to 2.5 (mean of these values: 2.0). The magnitude of the difference is larger with escitalopram than with citalopram.

Escitalopram demonstrated a significant early difference compared to placebo from week 2 onwards on the MADRS (week 1 in observed cases analysis). Likewise, the Clinical Global Impression–Improvement items (CGI-I) differed significantly from placebo from week 1 onwards. These early differences were not seen with racemic citalopram.

In the study with two parallel escitalopram dose groups, analysis of subgroups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D > 25) receiving 20 mg/day as compared to 10 mg/day. The Hamilton Rating Scale for Depression (HAM-D) consists of 17 to 24 items reflecting core symptoms of depression. Each item is scored on a 3, 4, or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

In a fourth flexible-dose study with a similar design, the primary analysis did not distinguish a significant drug/placebo difference for either escitalopram or citalopram over 8 weeks on the MADRS change score in the LOCF dataset. However, on the basis of the OC analysis, both escitalopram and citalopram were significantly better than placebo ($p \leq 0.05$; difference between escitalopram and placebo: 2.9).

Escitalopram demonstrated efficacy in the treatment of anxiety symptoms associated with depression. In the three positive double-blind placebo-controlled studies escitalopram was shown to be effective compared to placebo on the MADRS anxiety items; inner tension and sleep disturbances. Furthermore, in the one study where the Hamilton Anxiety Scale (HAM-A) and the anxiety factor of the Hamilton Depression Rating Scale (HAM-D scale) were used, results have shown that escitalopram was significantly better than placebo.

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open-label treatment phase with escitalopram 10 or 20 mg/day, were randomised to continuation of escitalopram at the same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined as a decrease of the MADRS total score to ≤ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo (26% vs. 40%; hazard ratio=0.56, p=0.013).

Further evidence of long-term efficacy is provided in a 6-month study which compared escitalopram 10 mg/day to citalopram 20 mg/day over a 6-month treatment period. Analysis of the primary endpoint (the development of the MADRS total scores over 24 weeks) demonstrated escitalopram to be at least as efficacious as citalopram in the long-term treatment of depression. Secondary analyses showed that, while both treatments resulted in numerical improvements in ratings in the MADRS, HAM-A and the CGI, escitalopram was statistically superior to citalopram in several analyses, both during and at the end of the study.

Additional supportive evidence of the sustained efficacy of escitalopram treatment is demonstrated in an open-label 12-month study. The efficacy of escitalopram was maintained throughout the study, as measured by the MADRS total score and CGI-S score. Patients showed continued improvement, with total MADRS scores falling from 14.2 at baseline to 5.8 at last assessment, and CGI-scores falling from 2.7 at baseline to 1.6 at last assessment.

A study in the elderly did not provide conclusive efficacy results for escitalopram, as the reference drug (fluoxetine) failed to differentiate from placebo. However, safety data from this study showed escitalopram to be well tolerated.

Generalised Anxiety Disorder (GAD)

LEXAPRO should not be used in the treatment of children and adolescents under the age of 18 years.

The efficacy of escitalopram in the treatment of Generalised Anxiety Disorder was demonstrated in three 8-week placebo-controlled flexible-dose studies (10 to 20 mg per day) and one 12-week fixed-dose, active-reference (paroxetine 20 mg/day), study (5, 10 and 20 mg per day).

In the four studies, the mean HAM-A total scores at baseline ranged from 22.1 to 27.7 and the CGI-S scores were 4.2 or higher, indicating significant GAD symptomatology.

In all three placebo-controlled, flexible-dose studies, escitalopram was significantly better than placebo at endpoint on the primary efficacy measure (mean change from baseline to endpoint in HAM-A total score), and the results were supported by secondary efficacy measures.

In the fixed-dose study, over a 12-week period, escitalopram in doses of 10 and 20 mg/day was statistically significantly more effective than placebo on the primary measure of efficacy, with an effect size at least as high as that of the reference treatment paroxetine. The 5 mg dose of escitalopram was numerically, but not statistically significantly, superior to placebo. 10 mg escitalopram was statistically significantly superior to the reference treatment paroxetine (LOCF) based on the HAM-A and CGI-I.

Table 1

Study	Mean Treatment Difference in Change from Baseline in HAM-A Total Scores (LOCF) [95% CI]	
	8 weeks	**12 weeks**
Flexible-dose		
ESC to PBO	-1.6*[-3.2; -0.0]	-
Flexible-dose		
ESC to PBO	-1.48*[-2.83; -0.13]	-
Flexible-dose		
ESC to PBO	-3.49***[-4.93; -2.04]	-
Fixed-dose		
ESC5 to PBO	-	-1.29 [-3.13; 0.54]
ESC10 to PBO	-	-2.56** [-4.40; -0.73]
ESC20 to PBO	-	-2.15* [-3.99; -0.31]
PAR20 to PBO	-	-0.51 [-2.33; 1.32]
ESC20 to PAR20	-	-1.65# [-3.49; 0.20]

*p≤0.05; **p≤0.01; ***p≤0.001; #p≤0.05 *versus* PAR

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

In the pooled analysis of these three placebo-controlled, flexible-dose studies of similar design, the mean change from baseline in HAM-A total score improved statistically significantly (LOCF) over time in the escitalopram group relative to the placebo group. The separation from placebo was first observed at week 1 and continued through to the end of the study (week 8). The treatment difference to placebo at week 8 was –2.3 in favour of escitalopram (p≤0.01).

The results of the primary analysis (pooled data) were supported by secondary LOCF analyses (pooled data), where escitalopram was statistically significantly superior to placebo on the HAM-A psychic anxiety subscale score (p≤0.001), the HAM-A item 1 (anxious mood) score (p≤0.001), and the HAM-A item 2 (tension) score (p≤0.01). Escitalopram was also more effective than placebo on the CGI-S score (p≤0.01) and on the CGI-I score at week 8 (p≤0.001). The results on the HAD anxiety subscale, the HAM-A somatic subscale, the HAM-D anxiety scale, the Covi Anxiety Scale (OC), and the QoL (OC) also showed superior efficacy of escitalopram relative to placebo at week 8 (p≤0.05).

The long-term efficacy of escitalopram in the treatment of GAD is based on the results from the double-blind active comparator study, an open-label extension study and a double-blind, randomised, placebo-controlled relapse prevention study.

The active comparator study demonstrated numerically superior efficacy of escitalopram over paroxetine both on the primary efficacy measure (mean change from baseline in HAM-A total score) and on the secondary efficacy measures (mean change from baseline

in HAM-A psychic anxiety, CGI-S, QoL, HAM-A somatic anxiety, HAM-A item 1 (anxious mood), HAM-A item 2 (tension), HAM-D anxiety and Covi scores, and mean CGI-I score) at week 24. For all but one (QoL) of the efficacy measures, a further improvement was seen from week 8 to week 24. In the primary efficacy analysis, the extra improvement in mean HAM-A total score over the last 16 weeks of treatment was 2.3 points for escitalopram compared with 1.6 points for paroxetine.

Further evidence of long-term efficacy is provided by an open-label extension study, which showed a beneficial effect of continued treatment with escitalopram. In this study, escitalopram treatment was associated with additional improvement beyond the response observed during the initial 8 weeks of treatment in the lead-in studies. The mean change in HAM-A total score from baseline (final visit of the lead-in study) to week 24 (LOCF) was -3.8, with greater improvement observed in patients who were switched from placebo in the lead-in study to escitalopram in the extension study (4.9 points versus 2.7 points for those previously treated with escitalopram). Similar positive results were seen in the analyses of secondary efficacy measures.

Escitalopram 20 mg/day significantly reduced the risk of relapse in a 24- to 76-week randomised continuation study in 373 patients who had responded during the initial 12-week open-label treatment.

Social Anxiety Disorder (SAD)

LEXAPRO should not be used in the treatment of children and adolescents under the age of 18 years.

The efficacy of escitalopram in the treatment of SAD was demonstrated in three placebo-controlled clinical studies. A short-term, flexible-dose (10 to 20 mg/day) study, a long-term, fixed-dose (5, 10, and 20 mg/day), active-reference (paroxetine 20 mg/day) study, and a relapse prevention study.

Approximately two-thirds of patients in the studies were markedly or severely ill (score of 5 or 6 on the CGI-S) and one-third were moderately ill (score of 4 or less on the CGI-S). The mean baseline LSAS total score ranged from 92 to 96 in the three studies.

In the short-term, flexible-dose study, over a 12-week period, escitalopram was statistically significantly better than placebo on the primary, and almost all the secondary measures of efficacy (see Table 2).

In the placebo-controlled, active-reference study, escitalopram was effective both in the short- and in the long-term (see Table 2), with an effect size at least as high as that of the reference treatment paroxetine (escitalopram 20 mg/day was significantly superior to the reference treatment paroxetine 20 mg/day from week 16 and onwards (OC)). Thus, continued treatment with escitalopram improves treatment response. At week 24 of the study, all three doses of escitalopram also produced significant improvements in the LSAS subscale scores for fear/anxiety and avoidance, the CGI-I score (except for the 10 mg dose of escitalopram), the CGI-S score, and the SDS subscale scores for work, social life, and family life.

Table 2

Study	Mean Treatment Difference in Change from Baseline in LSAS Total Scores (LOCF) [95% CI]	
	12 weeks	24 weeks
Short-term, flexible-dose		
ESC to PBO	-7.29** [-12.37; -2.21]	-
Long-term, fixed-dose		
ESC5 to PBO	-9.18*** [-14.40; -3.95]	-10.46*** [-16.27; -4.66]
ESC10 to PBO	-5.07† [-10.32; 0.18]	-7.45** [-13.29; -1.62]
ESC20 to PBO	-10.31*** [-15.56; -5.06]	-15.09*** [-20.92; -9.25]
PAR20 to PBO	-9.83*** [-15.04; -4.61]	-11.82*** [-17.62; -6.03]
ESC20 to PAR20	-	-3.26 [-9.07; 2.54]

*p≤0.05; **p≤0.01; ***p≤0.001; †p=0.059

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

The beneficial effect of long-term treatment with escitalopram was also reflected in the analyses of responders and remitters in this study. The analyses showed a further increase both in the proportion of responders and in the proportion of remitters from week 12 to week 24, especially in the escitalopram 20 mg group. At week 24, a statistically significantly greater proportion of responders and remitters were seen in all three escitalopram dose groups (except for the proportion of responders in the 10 mg group) than in the placebo group (p≤0.01) (see Tables 3 and 4).

Table 3

Long-term, fixed-dose study	Responders (CGI-I ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	41	50
ESC5	61***	67**
ESC10	55*	58
ESC20	62***	70***

*p≤0.05; **p≤0.01; ***p≤0.001

ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 4

Long-term, fixed-dose study	Remitters (CGI-S ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	13	19
ESC5	29***	39***
ESC10	24*	37***
ESC20	27**	46***

*p≤0.05; **p≤0.01; ***p≤0.001

ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

In the relapse prevention study, the primary efficacy analysis showed a statistically significantly superior effect of escitalopram relative to placebo on the time to relapse of SAD (log-rank test, p≤0.001). Furthermore, patients treated with escitalopram had fewer protocol-defined relapses than those treated with placebo. In addition, patients treated with escitalopram showed a further improvement in mean LSAS total score during the double-blind period, while patients treated with placebo showed deterioration. Escitalopram was also statistically significantly superior to placebo at week 24 on all the secondary efficacy measures in this study: the LSAS total score, the LSAS subscale scores for fear/anxiety and avoidance, the CGI-S score, and the SDS subscale scores for work, social life, and family life (p≤0.001).

Obsessive-Compulsive Disorder (OCD)

LEXAPRO should not be used in the treatment of children and adolescents under the age of 18 years.

Efficacy of escitalopram in the treatment of OCD was investigated in two clinical trials, a 24-week placebo-controlled, fixed-dose study (with efficacy assessments at week 12 and week 24) and a 16 + 24-week placebo-controlled relapse prevention study.

Patients included in these studies were male and female outpatients aged 18 – 65 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria and a pre-defined minimum score of 20 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Patients had actual baseline Y-BOCS scores of approx. 27, indicating significant OCD symptomatology. A structured clinical interview, the Mini International Neuropsychiatric Interview (MINI), was used to assist in the diagnosis and to exclude relevant psychiatric comorbidities. In order to avoid the confounding variable of significant concomitant depression, patients with more than mild depressive symptoms, i.e. a score of 22 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS), were excluded. To ensure a relatively homogenous population with OCD, patients currently diagnosed with any other psychiatric disorders as per Axis I of DSM-IV-TR or any clinically significant unstable medical illness were also excluded.

Results at week 12 of the 24-week placebo-controlled, fixed-dose study are shown in Tables 5 and 6. In the short-term (12 weeks), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score.

Table 5

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 12 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]
ESC10 to PBO	-1.97 [-3.97; 0.02]
ESC20 to PBO	-3.21* [-5.19; -1.23]

*p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Furthermore, escitalopram 20 mg/day was significantly more efficacious than placebo on the Y-BOCS subscale of rituals at week 12. Both escitalopram 10 mg/day and escitalopram 20 mg/day were significantly more efficacious than placebo on the Y-BOCS subscale of obsessions as well as on the NIMH-OCS total score, CGI-I score and CGI-S score.

Table 6

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 12 (FAS, LOCF, ANCOVA) [95% CI]				
	Y-BOCS Obsessional Subscore	Y-BOCS Compulsive Subscore	NIMH-OCS Score	CGI-I Score	CGI-S Score
ESC10 to PBO	-1.15* [-2.20; -0.10]	-1.01 [-2.04; 0.01]	-1.01** [-1.70; -0.33]	-0.36* [-0.66; -0.06]	-0.41* [-0.72; -0.09]
ESC20 to PBO	-2.05*** [-3.10; -1.01]	-1.34** [-2.37; -0.32]	-1.40*** [-2.08; -0.72]	-0.53*** [-0.83; -0.23]	-0.64*** [-0.95; -0.33]

*p≤0.05; **p≤0.01; ***p≤0.001
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Results after 24 weeks showed that both escitalopram 10 mg/day ($p<0.05$) and escitalopram 20 mg/day ($p<0.01$) were significantly more efficacious than placebo as measured by the primary outcome measure, the Y-BOCS total score, as well as on the secondary subscales of Y-BOCS (obsessions and rituals) and the NIMH-OCS score (escitalopram 10 mg/day ($p<0.01$) and escitalopram 20 mg/day ($p<0.001$)).

Table 7

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 24 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]
ESC10 to PBO	-2.56* [-4.93; -0.20]
ESC20 to PBO	-3.55** [-5.90; -1.20]

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

The beneficial efficacy of long-term treatment with escitalopram was also demonstrated by the analyses of responders and remitters in this study as shown in Tables 8 and 9.

Table 8

Long-term (24 weeks) fixed-dose study	Responders (CGI-I ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	38.9	38.1
ESC10	50	58*
ESC20	57.9*	56.1*

ESC (10 or 20 mg) vs PBO: *p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 9

Long-term (24 weeks) fixed-dose study	Remitters (CGI-S ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	11.5	26.5
ESC10	24.1*	41.1*
ESC20	28.1**	38.6

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Maintenance of efficacy and prevention of relapse were investigated in the relapse prevention study. This 24-week relapse prevention study was preceded by a 16-week open-label period with patients initially receiving escitalopram 10 mg/day. In case of lack of efficacy (as judged by the investigator), the dose could be increased to a maximum of 20 mg/day. If dose-limiting adverse effects occurred, it was permissible to decrease the dose to 10 mg/day. Thus the dose of escitalopram was flexible at 10 - 20 mg/day from week 2 to 12. Subsequently, the dose was fixed at the dose received at the end of week 12 until week 16 to allow stabilisation of the patient on this dose. Responders to treatment were defined as patients with a decrease in Y-BOCS total score from baseline by ≥ 25% at week 16, and remitters were defined as Y-BOCS ≤ 10. See Table 10 for responder and remitter rates at the end of the 16-week open-label phase.

Table 10

Relapse prevention study (16-week open-label, flexible-dose phase) (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF)	Responders (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF) (%)	Remitters (Y-BOCS ≤ 10) (APTS I, LOCF) (%)
ESC	74.4	34.0

ESC = escitalopram 10 & 20 mg

Responders at the end of the above 16-week open-label treatment phase (escitalopram 10 mg: 30 responders; escitalopram 20 mg: 133 responders) entered the 24-week randomised, double-blind placebo-controlled relapse prevention phase. Both escitalopram 10 mg/day (p=0.014) and 20 mg/day (p<0.001) showed significantly fewer relapses as seen in Table 11.

Table 11

Relapse prevention study (24-week double-blind phase)		n	Number of relapses	% relapsed
10 mg dose group	ESC10	30	3	10.00*
	PBO	20	7	35.00
20 mg dose group	ESC20	133	35	26.32**
	PBO	137	74	54.01
10 - 20 mg dose group	ESC	163	38	23.31**
	PBO	157	81	51.59

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.001
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; ESC = escitalopram 10 & 20 mg; PBO = placebo

INDICATIONS

Treatment of major depression.
Treatment of social anxiety disorder (social phobia).
Treatment of generalised anxiety disorder.
Treatment of obsessive-compulsive disorder.

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in LEXAPRO (see DESCRIPTION).

Monoamine Oxidase Inhibitors **-** LEXAPRO should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI, and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. Similarly, at least 14 days should be allowed after stopping escitalopram before starting a MAOI or RIMA. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see PRECAUTIONS, Interactions with other medicines).

Pimozide **-** Concomitant use in patients taking pimozide is contraindicated (see Interactions with other medicines).

PRECAUTIONS

Clinical worsening and suicide risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms are present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16-week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 trials), obsessive-compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either

worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for LEXAPRO should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Haemorrhage

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). LEXAPRO should therefore be used with caution in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Hyponatraemia

Probably due to inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia has been reported as a rare adverse reaction with the use of SSRIs. Especially elderly patients seem to be a risk group.

Seizures

The drug should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency (see Preclinical safety).

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Mania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

ECT (electroconvulsive therapy)

There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advised.

Effects on ability to drive and use machines

Escitalopram does not impair intellectual function and psychomotor performance. However, as with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

Discontinuation

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.

The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 - 3 months or more). It is therefore advised that escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see DOSAGE AND ADMINISTRATION).

Cardiac disease

Escitalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, escitalopram causes a small decrease in heart rate. Consequently, caution should be observed when escitalopram is initiated in patients with pre-existing slow heart rate.

Impaired hepatic function

In subjects with hepatic impairment, clearance of escitalopram was decreased and plasma concentrations were increased. The dose of escitalopram in hepatically impaired patients should therefore be reduced (see Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Impaired renal function

Escitalopram is extensively metabolised and excretion of unchanged drug in urine is a minor route of elimination. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) and escitalopram should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Preclinical safety

High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least 8-fold greater than anticipated clinically, have been associated with convulsions, ECG abnormalities and cardiovascular changes in experimental animals. Of the cardiovascular changes, cardiotoxicity (including congestive heart failure) was observed in comparative toxicological studies in rats following oral escitalopram or citalopram administration for 4 to 13 weeks and appears to correlate with peak plasma concentrations although its exact mechanism is not clear. Clinical experiences with citalopram, and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Carcinogenicity

No carcinogenicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

Citalopram did not show any carcinogenic activity in long-term oral studies using mice and rats at doses up to 240 and 80 mg/kg/day, respectively.

Genotoxicity

No genotoxicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

Effects on fertility

No fertility studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Animal data have shown that some SSRIs induce a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm. No animal data related to this aspect are available for escitalopram.

Animal data have shown that some SSRIs may affect sperm quality.

Use in pregnancy

Category C.

Limited clinical data are available regarding exposure to escitalopram during pregnancy.

Newborns should be observed if maternal use of LEXAPRO continues into the later stages of pregnancy, particularly in the third trimester. If escitalopram is used until or shortly before birth, discontinuation effects in the newborn are possible.

Newborns exposed to LEXAPRO, other SSRIs (Selective Serotonin Reuptake Inhibitors), or SNRIs (Serotonin Norepinephrine Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In the majority of cases the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological studies have shown that the use of SSRI's (including escitalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher than the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased post-implantation loss and reduced foetal weight at systemic exposure levels (based on AUC) ca. 11-fold that anticipated clinically, with no effects seen at 6-fold. No teratogenicity was evident in this study at relative systemic exposure levels of ca. 15 (based on AUC).

There were no peri/postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) ca. 2-fold that

anticipated clinically. However, the number of stillbirths was increased and the size, weight and postnatal survival of offspring were decreased at a relative systemic exposure level ca. 5.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit.

Use in lactation

It is expected that escitalopram, like citalopram, will be excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4 - 5.1% (below the notional 10% level of concern).

Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use of escitalopram in breast-feeding women, the decision to breast-feed should always be made as an individual risk/benefit analysis.

Paediatric use (children and adolescents < 18 years)

The efficacy and safety of escitalopram has not been established in children and adolescents less than 18 years of age. Consequently, escitalopram should not be used in children and adolescents less than 18 years of age.

Use in the elderly (> 65 years)

Escitalopram AUC and half-life were increased in subjects ≥ 65 years of age compared to younger subjects in a single-dose and a multiple-dose pharmacokinetic study. The dose of escitalopram in elderly patients should therefore be reduced (see DOSAGE AND ADMINISTRATION).

INTERACTIONS WITH OTHER MEDICINES

MAOIs

Co-administration with MAO inhibitors may cause serotonin syndrome (see CONTRAINDICATIONS).

Serotonin syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with escitalopram should be discontinued if such events occur and supportive symptomatic treatment initiated.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although

not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction with citalopram noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see CONTRAINDICATIONS).

Serotonergic drugs

Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, Hypericum perforatum (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and tryptophan

There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Medicines affecting the central nervous system

Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines lowering the seizure threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol).

Hepatic enzymes

Escitalopram has a low potential for clinically significant drug interactions. In vitro studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A4, and a weak inhibitor of 2D6.

Effects of other drugs on escitalopram in vivo

The pharmacokinetics of escitalopram was not changed by co-administration with ritonavir (CYP3A4 inhibitor). Furthermore, co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Co-administration of escitalopram with omeprazole (a CYP2C19 inhibitor) resulted in a moderate (approximately 50%) increase in plasma concentrations of escitalopram and a small but statistically significant increase (31%) in the terminal half-life of escitalopram (see also Poor metabolisers of CYP2C19 under DOSAGE AND ADMINISTRATION).

Co-administration of escitalopram with cimetidine (moderately potent general enzyme inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluoxetine,

fluvoxamine, lansoprazole, and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement (see also Poor metabolisers of CYP2C19 under DOSAGE AND ADMINISTRATION).

Effects of escitalopram on other drugs *in vivo*

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with metoprolol (a CYP2D6 substrate) resulted in a twofold increase in the plasma levels of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with escitalopram.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin, etc…)

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with LEXAPRO.

Alcohol

The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse reactions observed with escitalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually decrease in intensity and frequency with continued treatment and generally do not lead to a cessation of therapy. Data from short-term placebo-controlled studies are presented below. The safety data from the long-term studies showed a similar profile.

Treatment Emergent Adverse Events with an Incidence of ≥ 1% in placebo-controlled trials

Figures marked with * in the table below indicate adverse reactions where the incidence with escitalopram is statistically significantly different from placebo (p<0.05).

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
Patients Treated	1795	2632
Patients with Treatment Emergent Adverse Event	1135 (63.2)	1891 (71.8)
GASTROINTESTINAL SYSTEM DISORDERS		
nausea	151 (8.4)	481 (18.3)*
diarrhoea	91 (5.1)	207 (7.9)*
mouth dry	74 (4.1)	152 (5.8)*
constipation	42 (2.3)	71 (2.7)
abdominal pain	47 (2.6)	68 (2.6)
vomiting	29 (1.6)	54 (2.1)
dyspepsia	30 (1.7)	33 (1.3)
flatulence	15 (0.8)	31 (1.2)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS		
headache	305 (17.0)	506 (19.2)
dizziness	64 (3.6)	147 (5.6)*
paraesthesia	13 (0.7)	35 (1.3)
migraine	17 (0.9)	23 (0.8)
tremor	15 (0.8)	33 (1.3)
PSYCHIATRIC DISORDERS		
insomnia	82 (4.6)	245 (9.3)*
somnolence	62 (3.5)	217 (8.2)*
anorexia	12 (0.7)	56 (2.1)*
libido decreased	21 (1.2)	102 (3.9)*
anxiety	44 (2.5)	77 (2.9)
appetite decreased	8 (0.5)	35 (1.3)*
agitation	6 (0.3)	33 (1.3)*
nervousness	13 (0.7)	25 (1.0)
dreaming abnormal	18 (1.0)	41 (1.6)
impotence [gs]	4 (0.6)	22 (2.2)*
RESPIRATORY SYSTEM DISORDERS		
upper respiratory tract infection	91 (5.1)	96 (3.6)
coughing	18 (1.1)	24 (0.9)
rhinitis	81 (4.8)	146 (5.5)
sinusitis	24 (1.3)	46 (1.7)
pharyngitis	44 (2.5)	57 (2.2)
yawning	3 (0.2)	58 (2.2)*
bronchitis	31 (1.7)*	26 (0.9)

BODY AS A WHOLE - GENERAL DISORDERS		
influenza-like symptoms	65 (3.6)	87 (3.3)
fatigue	62 (3.5)	230 (8.7)*
back pain	61 (3.4)	74 (2.8)
SKIN AND APPENDAGES DISORDERS		
sweating increased	27 (1.5)	145 (5.5)*
MUSCULOSKELETAL SYSTEM DISORDERS		
arthralgia	22 (1.2)	27 (1.0)
REPRODUCTIVE DISORDERS, FEMALE		
anorgasmia [gs]	3 (0.3)	47 (2.9)*
METABOLIC AND NUTRITIONAL DISORDERS		
weight increase	20 (1.1)	45 (1.7)
REPRODUCTIVE DISORDERS, MALE		
ejaculation disorder [gs]	3 (0.5)	48 (4.7)*
ejaculation failure [gs]	1 (0.2)	27 (2.7)*
CARDIOVASCULAR DISORDERS		
hypertension	24 (1.3)*	13 (0.5)
HEART RATE AND RHYTHM DISORDERS		
palpitation	15 (0.8)	30 (1.1)
SECONDARY TERMS		
inflicted injury (unintended injury)	22 (1.2)	23 (0.8)

* = Statistically significant difference escitalopram vs placebo ($p<0.05$) [gs] = gender specific

Adverse Events in Relation to Dose

The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg escitalopram groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg escitalopram treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day escitalopram treated patients was greater (86%). Common adverse events that occurred in the 20 mg/day escitalopram group with an incidence approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group are shown overleaf.

Incidence of common adverse events* in patients with major depression receiving placebo, 10 mg/day Lexapro, or 20 mg/day Lexapro			
Adverse Event	**Placebo (n=311)**	**10 mg/day Lexapro (n=310)**	**20 mg/day Lexapro (n=125)**
Insomnia	4%	7%	14%
Diarrhoea	5%	6%	14%
Dry mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating increased	< 1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*adverse events with an incidence rate of at least 5% in either escitalopram group and with an incidence rate in the 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group reported.

Vital Sign Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment.

ECG Changes

Cases of QT prolongation have been reported during the post-marketing period with both citalopram and escitalopram. Citalopram can cause dose-dependent QT interval prolongation. In an ECG study, the observed change from baseline QT_C (Fridericia correction) was 7.5 msec at the 20mg/day dose and 16.7 msec at the 60mg/day dose of citalopram. The effect of escitalopram on the QT interval was similarly studied at doses of 10mg/day and 30mg/day. The change from baseline QTc (Fridericia correction) was 4.3 msec at the 10mg/day dose and 10.7 msec with the above recommended dose of 30mg/day. The QTc interval prolongation observed with 60mg citalopram exceeded that observed with 30mg escitalopram. It is probable that the R-enantiomer and its metabolites in racemic citalopram contribute to these effects.

Weight Changes

Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

In clinical studies, there were no signals of clinically important changes in either various serum chemistry, haematology, and urinalysis parameters associated with escitalopram treatment compared to placebo or in the incidence of patients meeting the criteria for potentially clinically significant changes from baseline in these variables.

For abnormal laboratory changes registered as either uncommon events or serious adverse events from ongoing trials and observed during (but not necessarily caused by) treatment

with Lexapro, please see Other Events Observed during the Premarketing Evaluation of Lexapro.

Other Events Observed during the Premarketing Evaluation of Lexapro

Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1% and serious adverse events from ongoing trials. All reported events are included except those already listed in the table or elsewhere in the Adverse Effects section, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients.

Application Site Disorders

Uncommon: otitis externa, cellulitis.

Body as a Whole
Uncommon: allergy, aggravated allergy, allergic reactions, asthenia, carpal tunnel syndrome, chest pain, chest tightness, fever, hernia, leg pain, limb pain, neck pain, oedema, oedema of extremities, peripheral oedema, rigors, malaise, syncope, scar.

Cardiovascular Disorders, General

Uncommon: hypertension aggravated, hypotension, hypertension, abnormal ECG.

Central and Peripheral Nervous System Disorders

Uncommon: ataxia, dysaesthesia, dysequilibrium, dysgeusia, dystonia, hyperkinesia, hyperreflexia, hypertonia, hypoaesthesia, leg cramps, lightheadedness, muscle contractions, nerve root lesion, neuralgia, neuropathy, paralysis, sedation, tetany, tics, twitching, vertigo.

Gastrointestinal System Disorders

Uncommon: abdominal cramp, abdominal discomfort, belching, bloating, change in bowel habit, colitis, colitis ulcerative, enteritis, epigastric discomfort, gastritis, gastroesophageal reflux, haemorrhoids, heartburn, increased stool frequency, irritable bowel syndrome, melaena, periodontal destruction, rectal haemorrhage, tooth disorder, toothache, ulcerative stomatitis.

Hearing and Vestibular Disorders

Uncommon: deafness, earache, ear disorder, otosalpingitis, tinnitus.

Heart Rate and Rhythm Disorders

Uncommon: bradycardia, tachycardia.

Liver and Biliary System Disorders

Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and Nutritional Disorders

Uncommon: abnormal glucose tolerance, diabetes mellitus, gout, hypercholesterolaemia, hyperglycaemia, hyperlipaemia, thirst, weight decrease, xerophthalmia.

Musculoskeletal System Disorders

Uncommon: arthritis, arthropathy, arthrosis, bursitis, costochondritis, fascitis plantar, fibromyalgia, ischial neuralgia, jaw stiffness, muscle cramp, muscle spasms, muscle stiffness, muscle tightness, muscle weakness, myalgia, myopathy, osteoporosis, pain neck/shoulder, tendinitis, tenosynovitis.
Myo-, Endo- and Pericardial and Valve Disorders

Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm

Uncommon: female breast neoplasm, ovarian cyst, uterine fibroid.

Platelet, Bleeding and Clotting Disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Poison Specific Terms

Uncommon: sting.

Psychiatric Disorders

Uncommon: aggressive reaction, amnesia, apathy, bruxism, carbohydrate craving, concentration impairment, confusion, depersonalisation, depression, depression aggravated, emotional lability, excitability, feeling unreal, forgetfulness, hallucination, hypomania, increased appetite, irritability, jitteriness, lethargy, loss of libido, obsessive-compulsive disorder, panic reaction, paroniria, restlessness aggravated, sleep disorder, snoring, suicide attempt, thinking abnormal.

Red Blood Cell Disorders

Uncommon: anaemia hypochromic, anaemia.

Reproductive Disorders / Female

Uncommon: amenorrhoea, atrophic vaginitis, breast pain, genital infection, intermenstrual bleeding, menopausal symptoms, menorrhagia, menstrual cramps, menstrual disorder, premenstrual tension, postmenopausal bleeding, sexual function abnormality, unintended pregnancy, dysmenorrhoea, vaginal haemorrhage, vaginal candidiasis, vaginitis.

Reproductive Disorders / Male

Uncommon: ejaculation delayed, prostatic disorder.

Resistance Mechanism Disorders

Uncommon: moniliasis genital, abscess, infection, herpes simplex, herpes zoster, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis.

Respiratory System Disorders

Uncommon: asthma, dyspnoea, laryngitis, nasal congestion, nasopharyngitis, pneumonia, respiratory tract infection, shortness of breath, sinus congestion, sinus headache, sleep apnoea, tracheitis, throat tightness.

Skin and Appendages Disorders
Uncommon: acne, alopecia, dermatitis, dermatitis fungal, dermatitis lichenoid, dry skin, eczema, erythematous rash, furunculosis, onychomycosis, pruritus, psoriasis aggravated, rash, rash pustular, skin disorder, urticaria, verruca.

Secondary Terms

Uncommon: accidental injury, bite, burn, fall, fractured neck of femur, alcohol problem, traumatic haematoma, cyst, food poisoning, lumbar disc lesion, surgical intervention.

Special Senses Other, Disorders

Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS, vision blurred.

Urinary System Disorders

Uncommon: cystitis, dysuria, facial oedema, micturition frequency, micturition disorder, nocturia, polyuria, pyelonephritis, renal calculus, urinary frequency, urinary incontinence, urinary tract infection.

Vascular (Extracardiac) Disorders

Uncommon: cerebrovascular disorder, flushing, hot flush [gs], ocular haemorrhage, peripheral ischaemia, varicose vein, vein disorder, vein distended.

Vision Disorders

Uncommon: accommodation abnormal, blepharospasm, eye infection, eye pain, mydriasis, vision abnormal, vision blurred, visual disturbance.

White Cell and Reticuloendothelial System Disorders

Uncommon: leucopenia.

In addition the following adverse reactions have been reported with racemic citalopram (all of which have also been reported for other SSRIs):

Disorders of metabolism and nutrition

Hyponatraemia, inappropriate ADH secretion (both especially in elderly women).

Neurological disorders

Convulsions, convulsions grand mal and extrapyramidal disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and inco-ordination).

Skin disorders

Ecchymoses, angioedema.

Furthermore a number of adverse reactions have been listed for other SSRIs. Although these are not listed as adverse reactions for escitalopram or citalopram, it cannot be excluded that these adverse reactions may occur with escitalopram. These SSRI class reactions are listed below:

Cardiovascular disorders

Postural hypotension.

Hepatobiliary disorders

Abnormal liver function tests.

Neurological disorders

Movement disorders.

Psychiatric disorders

Mania, panic attacks.

Renal and urinary disorders

Urinary retention.

Reproductive disorders

Galactorrhoea.

Other Events Observed During the Postmarketing Evaluation of Escitalopram

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported in association with escitalopram treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the Adverse Effects section:

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental overdose, injury NOS, psychotic disorder.

In addition, although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment subsequent to the marketing of racemic citalopram and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, anaphylaxis, choreoathetosis, delirium, dyskinesia, epidermal necrolysis, erythema multiforme, gastrointestinal haemorrhage, haemolytic anaemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinaemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

Class effect

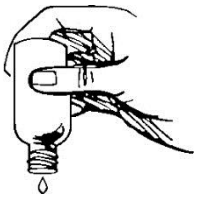
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

DOSAGE AND ADMINISTRATION

Adults

Escitalopram is administered as a single oral dose and may be taken with or without food.

The oral solution can be mixed with water, orange juice or apple juice.
Turn the bottle completely upside down. If no drops come out, tap the bottle lightly to start the flow.



Major depression

Usually 2 - 4 weeks are necessary for antidepressant response,
The recommended dose is 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 20 drops of the 20 mg/mL oral solution) daily. although the onset of therapeutic effect may be seen earlier. The treatment of a single episode of depression requires treatment over the acute and the medium term. After the symptoms resolve during acute treatment, a period of consolidation of the response is

required. Therefore, treatment of a depressive episode should be continued for a minimum of 6 months.

Social anxiety disorder

The recommended dose is 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 20 drops of the 20 mg/mL oral solution) daily. Social anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Generalised anxiety disorder

The recommended dose is 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 20 drops of the 20 mg/mL oral solution) daily. Generalised anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Obsessive-compulsive disorder

The recommended starting dose is 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) once daily. Depending on individual patient response, the dose may be increased to 20 mg (one 20 mg tablet or 20 drops of the 20 mg/mL oral solution) daily.

Long-term treatment has been studied for a maximum of 40 weeks. Patients responding to a 16-week open-label treatment phase were randomised to a 24-week placebo-controlled relapse prevention phase, receiving 10 or 20 mg escitalopram daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly patients (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) is the recommended maximum maintenance dose in the elderly (see Pharmacokinetics and PRECAUTIONS).

Children and adolescents (< 18 years of age)

Safety and efficacy have not been established in this population. Escitalopram should not be used in children and adolescents under 18 years of age (see PRECAUTIONS).

Reduced hepatic function

An initial dose of 5 mg (half a 10 mg tablet or 5 drops of the 20mg/mL oral solution) daily for the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) (see PRECAUTIONS).

Reduced renal function

Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) (see PRECAUTIONS).

Poor metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg (half a 10 mg tablet or 5 drops of the 20 mg/mL oral solution) daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet or 10 drops of the 20 mg/mL oral solution) (see Pharmacokinetics and Interactions with other medicines under PRECAUTIONS).

Discontinuation

Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over a period of at least one to two weeks is recommended. If unacceptable discontinuation symptoms occur following a decrease in the dose or upon discontinuation of treatment then resuming the previously prescribed dose may be considered. Subsequently, the dose may be decreased but at a more gradual rate.

OVERDOSAGE

In general, the main therapy for all overdoses is supportive and symptomatic care.

Toxicity

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Doses between 400 and 800 mg of escitalopram alone have been taken without any severe symptoms. No fatalities or sequelae were reported in the few cases with a higher dose (one patient survived ingestion of either 2,400 or 4,800 mg).

Symptoms

Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting), the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation), and electrolyte/fluid balance conditions.

Treatment

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

PRESENTATION AND STORAGE CONDITIONS

Lexapro tablets

- Film-coated tablets containing 10mg and 20 mg escitalopram (as oxalate)
- Blister packs of 7 and 28 tablets

Lexapro solution

20 mg/mL

- Oral solution containing 20 mg/mL escitalopram (as oxalate)
- 15 mL solution in brown glass bottle with a dropper applicator and childproof screw cap

Storage conditions

Lexapro tablets: Store below 30°C.
Lexapro oral solution: Store below 25°C.

Store the opened oral solution below 25°C.

Discard the 20 mg/mL oral solution 2 months after opening.

NAME AND ADDRESS OF THE SPONSOR

Lundbeck Australia Pty Ltd
Ground Floor
1 Innovation Rd
North Ryde NSW 2113
Ph: +61 2 8669 1000

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

16 September 2003

DATE OF MOST RECENT AMENDMENT

6th February 2018

Lexapro®

(LEX-a-pro) Oral Solution

Escitalopram oxalate (ES-sigh-talo-pram OX-a-late)

Consumer Medicine Information

What is in this leaflet

This leaflet contains answers to some common questions about LEXAPRO.

It does not contain all the information that is known about LEXAPRO. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risk of you using this medicine against the benefits he/she expects it will have for you.

If you have any concerns about using this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.

You may need to read it again

What LEXAPRO is used for

LEXAPRO is used to treat depression.

It belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). They are thought to work by their actions on brain chemicals called amines which are involved in controlling mood.

Depression is longer lasting or more severe than the "low moods" everyone has from time to time due to the stress of everyday life. It is thought to be caused by a chemical imbalance in parts of the brain. This imbalance affects your whole body and can cause emotional and physical symptoms such as feeling low in spirit, loss of interest in activities, being unable to enjoy life, poor appetite or overeating, disturbed sleep, often waking up early, loss of sex drive, lack of energy and feeling guilty over nothing.

LEXAPRO corrects this chemical imbalance and may help relieve the symptoms of depression.

LEXAPRO may also be used to treat patients who may avoid and/or are fearful of social situations.

LEXAPRO may also be used to treat patients who have excessive anxiety and worry.

LEXAPRO may also be used to treat irrational fears or obsessional behaviour (obsessive-compulsive disorder). Obsessive-compulsive disorder involves having both obsessions and compulsions. Obsessions are unwanted thoughts that occur over and over again. Compulsions are the ongoing need to repeat certain actions as a result of these thoughts.

Your doctor, however, may prescribe it for another purpose.

Ask your doctor if you have any questions about why it has been prescribed for you.

This medicine is only available with a doctor's prescription.

LEXAPRO is not addictive. However, if you suddenly stop taking it, you may get side effects.

Tell your doctor if you get any side effects after stopping LEXAPRO.

Before you take it

When you must not take it

Do not take LEXAPRO if you are allergic to it, to any medicine containing escitalopram, citalopram, or any of the ingredients listed at the end of this leaflet.

Symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, or rash, itching or hives on the skin.

Do not take LEXAPRO at the same time as the following other medicines:

- pimozide, a medicine used to treat mental disorders
- monoamine oxidase inhibitors (MAOIs), such as phenelzine, tranylcypromine and moclobemide which are also used for the treatment of depression.

  One day must elapse after you have finished taking moclobemide before you start taking LEXAPRO. If you have taken any other MAOI you will need to wait 14 days. After stopping LEXAPRO you must allow 14 days before taking any MAOI including moclobemide.

  Taking LEXAPRO with MAOIs may cause a serious reaction with a sudden increase in body temperature, extremely high blood pressure and severe

convulsions. Your doctor will know when it is safe to start LEXAPRO after the MAOI has been stopped.

Do not take it after the expiry date printed on the pack.

If you take it after the expiry date has passed, it may not work as well. The expiry date refers to the last day of the month.

Do not take it if the packaging is torn or shows signs of tampering

Before you start to take it

Tell your doctor if:

- **you have allergies to any other substances such as foods, preservatives or dyes.**
- **you are pregnant or intend to become pregnant.**

  Medicines like Lexapro have been shown to reduce the quality of sperm in animal studies, which theoretically could affect fertility. If you are intending to start a family, ask your doctor for advice.

  Do not take LEXAPRO if you are pregnant unless you and your doctor have discussed the risks and benefits involved.

  Make sure your doctor and/or midwife know you are on LEXAPRO.

  When taken during pregnancy, particularly in the last three months of pregnancy, medicines like LEXAPRO may affect the general condition of your newborn baby and may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your doctor and/or midwife immediately.

  If used during pregnancy LEXAPRO should never be stopped abruptly.
- **you are breast-feeding or planning to breast-feed.**

  Do not take LEXAPRO if you are breast-feeding unless you and your doctor have discussed the risks and benefits involved. It is not recommended that you breast-feed while taking LEXAPRO as it is excreted in breast milk.
- **you have, or have had, the following medical conditions:**
  - a tendency to bleed or bruise easily
  - diabetes
  - heart disease
  - kidney disease
  - liver disease
  - bipolar disorder (manic depression)
  - a history of seizures or fits
  - restlessness and/or a need to move often
- **you are receiving electroconvulsive therapy.**

Do not give LEXAPRO to a child or adolescent.

There is no experience with its use in children or adolescents under 18 years old.

LEXAPRO can be given to elderly patients over 65 years of age with a reduced dose.

The effects of LEXAPRO in elderly patients are similar to those in other patients.

If you have not told your doctor about any of the above, tell them before you use LEXAPRO.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and LEXAPRO may interfere with each other. These include:

- bupropion, a medicine helping to treat nicotine dependence
- medicines used to treat reflux and ulcers, such as cimetidine, omeprazole, esomeprazole and lansoprazole
- medicines known to prolong bleeding, e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
- ticlopidine and warfarin, medicines used to prevent blood clots
- mefloquine, an anti-malaria medicine
- sumatriptan, used to treat migraines
- tramadol, used to relieve pain
- medicines affecting the chemicals in the brain
- some heart medications, e.g. flecainide, propafenone, metoprolol
- tryptophan, an amino-acid
- lithium, used to treat mood swings and some types of depression
- antipsychotics, a class of medicines used to treat certain mental and emotional conditions, e.g. risperidone, thioridazine and haloperidol
- tricyclic antidepressants, e.g. imipramine, desipramine
- St John's Wort (Hypericum perforatum), a herbal remedy
- any other medicines for depression, anxiety, obsessive-compulsive disorder or pre-menstrual dysphoric disorder

These medicines may be affected by LEXAPRO, or may affect how well it works. You may need to use different amounts of your medicines, or take different medicines. Your doctor will advise you.

Some combinations of medicines may increase the risk of serious side

effects and are potentially life threatening.

Your doctor or pharmacist has more information on medicines to be careful with or avoid while taking LEXAPRO.

How to take it

How much to take

Your doctor will decide what dose you will receive.

The standard dose for this medicine is 10 mg per day. This may be increased by your doctor to 20 mg per day.

The recommended maximum dose in elderly patients is 10 mg per day.

It is recommended that patients with liver disease receive an initial dose of 5 mg daily for the first two weeks. Your doctor may increase the dose to 10 mg daily.

A 5 mg dose can be delivered by measuring 5 drops of LEXAPRO oral solution 20 mg/mL.

A 10 mg dose can be delivered by measuring 10 drops of LEXAPRO oral solution 20 mg/mL.

A 20 mg dose can be delivered by measuring 20 drops of LEXAPRO oral solution 20 mg/mL.

Your doctor may have prescribed a different dose.

Ask your doctor or pharmacist if you are unsure of the correct dose for you.

They will tell you exactly how much to take.

Follow the instructions they give you.

If you take the wrong dose, LEXAPRO may not work as well and your condition may not improve.

How to take it

Oral solution 20 mg/mL: Turn the bottle completely upside down. If no drops come out, tap the bottle lightly to start the flow.

Count the required number of drops into your drink (water, orange juice or apple juice), stir it briefly and then drink all of it.

Do not mix the LEXAPRO oral solution with other liquids and do not mix them with other medicinal products.

When to take it

Take LEXAPRO as a single dose either in the morning or in the evening.

Take LEXAPRO with or without food.

How long to take it

Continue to take LEXAPRO even if it takes some time before you feel any improvement in your condition.

As with other medicines for the treatment of these conditions it may take a few weeks before you feel any improvement.

Individuals will vary greatly in their response to LEXAPRO. Your doctor will check your progress at regular intervals.

The duration of treatment may vary for each individual, but is usually at least 6 months.

In some cases the doctor may decide that longer treatment is necessary.

Continue taking your medicine for as long as your doctor tells you, even if you begin to feel better.

The underlying illness may persist for a long time and if you stop your treatment too soon, your symptoms may return.

Do not stop taking this medicine suddenly.

If LEXAPRO is stopped suddenly you may experience mild, but usually temporary, symptoms such as dizziness, pins and needles, electric shock sensations, sleep disturbances (vivid dreams, inability to sleep), feeling anxious or agitated, headaches, feeling sick (nausea), vomiting, sweating, tremor (shaking), feeling confused, feeling emotional or irritable, diarrhoea, visual disturbances, or fast or irregular heartbeats.

When you have completed your course of treatment, the dose of LEXAPRO is gradually reduced over a couple of weeks rather than stopped abruptly.

Your doctor will tell you how to reduce the dosage so that you do not get these unwanted effects.

If you forget to take it

If you miss a dose and remember in less than 12 hours, take it straight away, and then go back to taking it as you would normally.

Otherwise, if it is almost time for your next dose, skip the dose you missed and take the next dose when you are meant to.

Do not take a double dose to make up for the dose you have missed.

If you are not sure what to do, ask your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for hints.

If you take too much (overdose)

Immediately telephone your doctor, or the Poisons Information Centre (Tel: 13 11 26), or go to Accident and Emergency at your nearest hospital, if you think you or anyone else may have taken too much LEXAPRO.

Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

Symptoms of an overdose may include dizziness, low blood pressure, nausea (feeling sick), vomiting, agitation, tremor (shaking) and rarely convulsions and coma.

While you are taking it

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking LEXAPRO.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you become pregnant while taking LEXAPRO, tell your doctor immediately.

Persons taking LEXAPRO may be more likely to think about killing themselves or actually trying to do so, especially when LEXAPRO is first started or the dose is changed. Tell your doctor immediately if you have thoughts about killing yourself or if you are close to or care for someone using LEXAPRO who talks about or shows signs of killing him or herself.

All mentions of suicide or violence must be taken seriously.

Occasionally, the symptoms of depression may include thoughts of suicide or self-harm. It is possible that these symptoms continue or get worse until the full antidepressant effect of the medicine becomes apparent. This is more likely to occur if you are a young adult, i.e. 18 to 24 years of age, and you have not used antidepressant medicines before.

Patients and care givers should pay attention for any of the following warning signs of suicide-related behaviour while taking LEXAPRO. Tell your doctor immediately, or even go to the nearest hospital for treatment:

- thoughts or talk of death or suicide
- thoughts or talk of self-harm or harm to others
- any recent attempts of self-harm
- increase in aggressive behaviour, irritability or agitation

Do not stop taking this medicine or change the dose without consulting your doctor, even if you experience increased anxiety at the beginning of treatment.

At the beginning of treatment, some patients may experience increased anxiety which will disappear during continued treatment.

Tell your doctor immediately if you experience symptoms such as restlessness or difficulty in sitting or standing still.

These symptoms can occur during the first weeks of treatment.

Contact your doctor as soon as possible if you suddenly experience an episode of mania.

Some patients with bipolar disorder (manic depression) may enter into a manic phase. This is characterised by profuse and rapidly changing ideas, exaggerated gaiety and excessive physical activity.

Sometimes you may be unaware of the above-mentioned symptoms and therefore you may find it helpful to ask a friend or relative to help you to observe the possible signs of change in your behaviour.

Things you must not do

Do not give the oral solution to anyone else, even if they have the same condition as you.

Do not take LEXAPRO to treat any other complaints unless your doctor tells you to.

Do not stop taking LEXAPRO, or lower the dosage, without checking with your doctor.

Do not let yourself run out of medicine over the weekend or on holidays.

Suddenly stopping LEXAPRO may cause unwanted discontinuation symptoms such as dizziness, headache and nausea. Your doctor will tell you when and how LEXAPRO should be discontinued. Your doctor will gradually reduce the amount you are using, usually over a period of one to two weeks, before stopping completely.

Things to be careful of

Be careful driving or operating machinery until you know how LEXAPRO affects you.

It may cause nausea, fatigue and dizziness in some people, especially early in the treatment. If you have any of these symptoms, do not drive, operate machinery, or do anything else that could be dangerous.

Avoid alcohol while you are taking this medicine.

It is not advisable to drink alcohol while you are being treated for depression.

Side effects

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time they are not. Your doctor has weighed the risks of using this medicine against the benefits he/she expects it will have for you.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking LEXAPRO.

It helps most people with depression, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder, but it may have unwanted side effects in a few people.

The side effects of LEXAPRO are, in general, mild and disappear after a short period of time.

Tell your doctor if you notice any of the following and they worry you:

- decreased appetite or loss of appetite

- dry mouth
- diarrhoea
- nausea (feeling sick)
- sleeplessness
- fatigue, sleepiness or drowsiness, yawning
- increased sweating
- sexual disturbances (decreased sexual drive; problems with ejaculation or erection; women may experience difficulties achieving orgasm)

*The side effects marked with an asterisk (*) are a number of rare side effects that are known to occur with medicines that work in a similar way to LEXAPRO.

Tell your doctor as soon as possible if you notice any of the following:

- agitation, confusion, panic attacks*, anxiety, restlessness*
- dizziness
- dizziness when you stand up due to low blood pressure*
- fast heart rate or decrease in heart rate or irregular heart beat
- low sodium levels in the blood (the symptoms are feeling sick and unwell with weak muscles or feeling confused)*
- abnormal liver function tests (increased amounts of liver enzymes in the blood)*
- difficulties urinating*
- unusual secretion of breast milk*
- bleeding disorders including skin and mucous bleeding (e.g. bruising*) and a low level of blood platelets*
- rash, itching, patches of circumscribed swellings
- an increased risk of bone fractures has been observed in patients taking this type of medicine*

These may be serious side effects of LEXAPRO. You may need urgent medical attention.

Tell your doctor immediately, or go to Accident and Emergency at your nearest hospital, if you notice any of the following:

- thoughts of harming yourself or thoughts of suicide*, see also section "Things you must do"
- serious allergic reaction (symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, or hives)
- high fever, agitation, confusion, trembling and abrupt contractions of muscles (these symptoms may be signs of a rare condition called serotonin syndrome)*
- mania (i.e.: elevated mood and associated symptoms)*
- hallucinations
- seizures, tremors, movement disorders (involuntary movements of the muscles)*
- fast, irregular heart beat with feelings of dizziness or difficulty breathing

These are very serious side effects. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

After taking it

Storage

Keep LEXAPRO oral solution in a cool dry place where the temperature stays below 25°C.

Discard LEXAPRO oral solution 20 mg/mL 2 months after first opening.

Do not store it or any other medicine in the bathroom, near a sink, or on a window-sill.

Do not leave it in the car.

Heat and damp can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking LEXAPRO, or the medicine has passed its expiry date, ask your pharmacist what to do with any that is left over.

Return any unused medicine to your pharmacist.

Product description

What it looks like

LEXAPRO oral solution is a clear, nearly colourless to yellowish solution.

LEXAPRO 20 mg/mL oral solution: 15 mL in a brown glass bottle with a dropper applicator and childproof screw cap.

Ingredients

Active ingredient(s):

- LEXAPRO oral solution 20 mg/mL: Each mL (20 drops) contains 20 mg escitalopram (as oxalate). One drop contains 1 mg escitalopram (as oxalate).

Inactive ingredients (oral solution 20 mg/mL):

- propyl gallate
- anhydrous citric acid
- ethanol/alcohol
- sodium hydroxide
- purified water

LEXAPRO oral solution does not contain lactose, gluten, sucrose, tartrazine or any other azo dyes.

Manufacturer/Sponsor

LEXAPRO is made by H. Lundbeck A/S, Denmark.

Distributed in Australia by:

Lundbeck Australia Pty Ltd

Ground Floor, 1 Innovation Road

North Ryde NSW 2113

Ph: +61 2 8669 1000

This leaflet was prepared on

10th January 2018.

Australian Registration Numbers:

LEXAPRO oral solution

20 mg/mL - AUST R 209721

"Lexapro" is the registered trade mark of H. Lundbeck A/S.

Lexapro®

(LEX-a-pro)
Tablets

Escitalopram oxalate (ES-sigh-talo-pram OX-a-late)

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Keep this leaflet with the medicine.

You may need to read it again

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LEXAPRO is used to treat depression.

It belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). They are thought to work by their actions on brain chemicals called amines which are involved in controlling mood.

Depression is longer lasting or more severe than the "low moods" everyone has from time to time due to the stress of everyday life. It is thought to be caused by a chemical imbalance in parts of the brain. This imbalance affects your whole body and can cause emotional and physical symptoms such as feeling low in spirit, loss of interest in activities, being unable to enjoy life, poor appetite or overeating, disturbed sleep, often waking up early, loss of sex drive, lack of energy and feeling guilty over nothing.

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LEXAPRO may also be used to treat patients who may avoid and/or are fearful of social situations.

LEXAPRO may also be used to treat patients who have excessive anxiety and worry.

LEXAPRO may also be used to treat irrational fears or obsessional behaviour (obsessive-compulsive disorder). Obsessive-compulsive disorder involves having both obsessions and compulsions. Obsessions are unwanted thoughts that occur over and over again. Compulsions are the ongoing need to repeat certain actions as a result of these thoughts.

Your doctor, however, may prescribe it for another purpose.

Ask your doctor if you have any questions about why it has been prescribed for you.

This medicine is only available with a doctor's prescription.

LEXAPRO is not addictive. However, if you suddenly stop taking it, you may get side effects.

Tell your doctor if you get any side effects after stopping LEXAPRO.

Before you take it

When you must not take it

Do not take LEXAPRO if you are allergic to it, to any medicine containing escitalopram, citalopram, or any of the ingredients listed at the end of this leaflet.

Symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, or rash, itching or hives on the skin.

Do not take LEXAPRO at the same time as the following other medicines:

- pimozide, a medicine used to treat mental disorders
- monoamine oxidase inhibitors (MAOIs), such as phenelzine, tranylcypromine and moclobemide which are also used for the treatment of depression.

  One day must elapse after you have finished taking moclobemide before you start taking LEXAPRO. If you have taken any other MAOI you will need to wait 14 days. After stopping LEXAPRO you must allow 14 days before taking any MAOI including moclobemide.

  Taking LEXAPRO with MAOIs may cause a serious reaction with a sudden increase in body temperature,

extremely high blood pressure and severe convulsions. Your doctor will know when it is safe to start LEXAPRO after the MAOI has been stopped.

Do not take it after the expiry date printed on the pack.

If you take it after the expiry date has passed, it may not work as well. The expiry date refers to the last day of the month.

Do not take it if the packaging is torn or shows signs of tampering

Before you start to take it

Tell your doctor if:

- **you have allergies to any other substances such as foods, preservatives or dyes.**
- **you are pregnant or intend to become pregnant.**

  Medicines like Lexapro have been shown to reduce the quality of sperm in animal studies, which theoretically could affect fertility. If you are intending to start a family, ask your doctor for advice.

  Do not take LEXAPRO if you are pregnant unless you and your doctor have discussed the risks and benefits involved.

  Make sure your doctor and/or midwife know you are on LEXAPRO.

  When taken during pregnancy, particularly in the last three months of pregnancy, medicines like LEXAPRO may affect the general condition of your newborn baby and may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your doctor and/or midwife immediately.

  If used during pregnancy LEXAPRO should never be stopped abruptly.

- **you are breast-feeding or planning to breast-feed.**

  Do not take LEXAPRO if you are breast-feeding unless you and your doctor have discussed the risks and benefits involved. It is not recommended that you breast-feed while taking LEXAPRO as it is excreted in breast milk.

- **you have, or have had, the following medical conditions:**
  - a tendency to bleed or bruise easily
  - diabetes
  - heart disease
  - kidney disease
  - liver disease
  - bipolar disorder (manic depression)
  - a history of seizures or fits
  - restlessness and/or a need to move often
- **you are receiving electroconvulsive therapy.**

Do not give LEXAPRO to a child or adolescent.

There is no experience with its use in children or adolescents under 18 years old.

LEXAPRO can be given to elderly patients over 65 years of age with a reduced dose.

The effects of LEXAPRO in elderly patients are similar to those in other patients.

If you have not told your doctor about any of the above, tell them before you use LEXAPRO.

Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines and LEXAPRO may interfere with each other. These include:

- bupropion, a medicine helping to treat nicotine dependence
- medicines used to treat reflux and ulcers, such as cimetidine, omeprazole, esomeprazole and lansoprazole
- medicines known to prolong bleeding, e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
- ticlopidine and warfarin, medicines used to prevent blood clots
- mefloquine, an anti-malaria medicine
- sumatriptan, used to treat migraines
- tramadol, used to relieve pain
- medicines affecting the chemicals in the brain
- some heart medications, e.g. flecainide, propafenone, metoprolol
- tryptophan, an amino-acid
- lithium, used to treat mood swings and some types of depression
- antipsychotics, a class of medicines used to treat certain mental and emotional conditions, e.g. risperidone, thioridazine and haloperidol
- tricyclic antidepressants, e.g. imipramine, desipramine
- St John's Wort (Hypericum perforatum), a herbal remedy
- any other medicines for depression, anxiety, obsessive-compulsive disorder or pre-menstrual dysphoric disorder

These medicines may be affected by LEXAPRO, or may affect how well it works. You may need to use different amounts of your medicines, or take different medicines. Your doctor will advise you.

Some combinations of medicines may increase the risk of serious side effects and are potentially life threatening.

Your doctor or pharmacist has more information on medicines to be careful with or avoid while taking LEXAPRO.

How to take it

How much to take

Your doctor will decide what dose you will receive.

The standard dose for this medicine is 10 mg per day. This may be increased by your doctor to 20 mg per day.

The recommended maximum dose in elderly patients is 10 mg per day.

It is recommended that patients with liver disease receive an initial dose of 5 mg daily for the first two weeks. Your doctor may increase the dose to 10 mg daily.

Your doctor may have prescribed a different dose.

Ask your doctor or pharmacist if you are unsure of the correct dose for you.

They will tell you exactly how much to take.

Follow the instructions they give you.

If you take the wrong dose, LEXAPRO may not work as well and your condition may not improve.

How to take it

Swallow the tablets whole with a full glass of water.

Do not chew them.

When to take it

Take LEXAPRO as a single dose either in the morning or in the evening.

Take LEXAPRO with or without food.

How long to take it

Continue to take LEXAPRO even if it takes some time before you feel any improvement in your condition.

As with other medicines for the treatment of these conditions it may take a few weeks before you feel any improvement.

Individuals will vary greatly in their response to LEXAPRO. Your doctor will check your progress at regular intervals.

The duration of treatment may vary for each individual, but is usually at least 6 months.

In some cases the doctor may decide that longer treatment is necessary.

Continue taking your medicine for as long as your doctor tells you, even if you begin to feel better.

The underlying illness may persist for a long time and if you stop your treatment too soon, your symptoms may return.

Do not stop taking this medicine suddenly.

If LEXAPRO is stopped suddenly you may experience mild, but usually temporary, symptoms such as dizziness, pins and needles, electric shock sensations, sleep disturbances (vivid dreams, inability to sleep), feeling anxious or agitated, headaches, feeling sick (nausea), vomiting, sweating, tremor (shaking), feeling confused, feeling emotional or irritable, diarrhoea, visual disturbances, or fast or irregular heartbeats.

When you have completed your course of treatment, the dose of LEXAPRO is gradually reduced over a couple of weeks rather than stopped abruptly.

Your doctor will tell you how to reduce the dosage so that you do not get these unwanted effects.

If you forget to take it

If you miss a dose and remember in less than 12 hours, take it straight away, and then go back to taking it as you would normally.

Otherwise, if it is almost time for your next dose, skip the dose you missed and take the next dose when you are meant to.

Do not take a double dose to make up for the dose you have missed.

If you are not sure what to do, ask your doctor or pharmacist.

If you have trouble remembering when to take your medicine, ask your pharmacist for hints.

If you take too much (overdose)

Immediately telephone your doctor, or the Poisons Information Centre (Tel: 13 11 26), or go to Accident and Emergency at your nearest hospital, if you think you or anyone else may have taken too much LEXAPRO.

Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

Symptoms of an overdose may include dizziness, low blood pressure, nausea (feeling sick), vomiting, agitation, tremor (shaking) and rarely convulsions and coma.

While you are taking it

Things you must do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking LEXAPRO.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you become pregnant while taking LEXAPRO, tell your doctor immediately.

Persons taking LEXAPRO may be more likely to think about killing themselves or actually trying to do so, especially when LEXAPRO is first started or the dose is changed.

Tell your doctor immediately if you have thoughts about killing yourself or if you are close to or care for someone using LEXAPRO who talks about or shows signs of killing him or herself.

All mentions of suicide or violence must be taken seriously.

Occasionally, the symptoms of depression may include thoughts of suicide or self-harm. It is possible that these symptoms continue or get worse until the full antidepressant effect of the medicine becomes apparent. This is more likely to occur if you are a young adult, i.e. 18 to 24 years of age, and you have not used antidepressant medicines before.

Patients and care givers should pay attention for any of the following warning signs of suicide-related behaviour while taking LEXAPRO. Tell your doctor immediately, or even go to the nearest hospital for treatment:

- thoughts or talk of death or suicide
- thoughts or talk of self-harm or harm to others
- any recent attempts of self-harm
- increase in aggressive behaviour, irritability or agitation

Do not stop taking this medicine or change the dose without consulting your doctor, even if you experience increased anxiety at the beginning of treatment.

At the beginning of treatment, some patients may experience increased anxiety which will disappear during continued treatment.

Tell your doctor immediately if you experience symptoms such as restlessness or difficulty in sitting or standing still.

These symptoms can occur during the first weeks of treatment.

Contact your doctor as soon as possible if you suddenly experience an episode of mania.

Some patients with bipolar disorder (manic depression) may enter into a manic phase. This is characterised by profuse and rapidly changing ideas, exaggerated gaiety and excessive physical activity.

Sometimes you may be unaware of the above-mentioned symptoms and therefore you may find it helpful to ask a friend or relative to help you to observe the possible signs of change in your behaviour.

Things you must not do

Do not give the tablets to anyone else, even if they have the same condition as you.

Do not take LEXAPRO to treat any other complaints unless your doctor tells you to.

Do not stop taking LEXAPRO, or lower the dosage, without checking with your doctor.

Do not let yourself run out of medicine over the weekend or on holidays.

Suddenly stopping LEXAPRO may cause unwanted discontinuation symptoms such as dizziness, headache and nausea. Your doctor will tell you when and how LEXAPRO should be discontinued. Your doctor will gradually reduce the amount you are using, usually over a period of one to two weeks, before stopping completely.

Things to be careful of

Be careful driving or operating machinery until you know how LEXAPRO affects you.

It may cause nausea, fatigue and dizziness in some people, especially early in the treatment. If you have any of these symptoms, do not drive, operate machinery, or do anything else that could be dangerous.

Avoid alcohol while you are taking this medicine.

It is not advisable to drink alcohol while you are being treated for depression.

Side effects

All medicines may have some unwanted side effects. Sometimes they are serious, but most of the time they are not. Your doctor has weighed the risks of using this medicine against the benefits he/she expects it will have for you.

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking LEXAPRO.

It helps most people with depression, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder, but it may have unwanted side effects in a few people.

The side effects of LEXAPRO are, in general, mild and disappear after a short period of time.

Tell your doctor if you notice any of the following and they worry you:

- decreased appetite or loss of appetite
- dry mouth
- diarrhoea
- nausea (feeling sick)
- sleeplessness
- fatigue, sleepiness or drowsiness, yawning
- increased sweating
- sexual disturbances (decreased sexual drive; problems with ejaculation or erection; women may experience difficulties achieving orgasm)

*The side effects marked with an asterisk (*) are a number of rare side effects that are known to occur with medicines that work in a similar way to LEXAPRO.

Tell your doctor as soon as possible if you notice any of the following:

- agitation, confusion, panic attacks*, anxiety, restlessness*
- dizziness
- dizziness when you stand up due to low blood pressure*
- fast heart rate or decrease in heart rate or irregular heart beat
- low sodium levels in the blood (the symptoms are feeling sick and unwell with weak muscles or feeling confused)*
- abnormal liver function tests (increased amounts of liver enzymes in the blood)*
- difficulties urinating*
- unusual secretion of breast milk*
- bleeding disorders including skin and mucous bleeding (e.g. bruising*) and a low level of blood platelets*
- rash, itching, patches of circumscribed swellings
- an increased risk of bone fractures has been observed in patients taking this type of medicine*

These may be serious side effects of LEXAPRO. You may need urgent medical attention.

Tell your doctor immediately, or go to Accident and Emergency at your nearest hospital, if you notice any of the following:

- thoughts of harming yourself or thoughts of suicide*, see also section "Things you must do"
- serious allergic reaction

  (symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, or hives)
- high fever, agitation, confusion, trembling and abrupt contractions of muscles

  (these symptoms may be signs of a rare condition called serotonin syndrome)*
- mania (i.e.: elevated mood and associated symptoms)*
- hallucinations
- seizures, tremors, movement disorders (involuntary movements of the muscles)*
- fast, irregular heart beat with feelings of dizziness or difficulty breathing

These are very serious side effects. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice anything else that is making you feel unwell.

Other side effects not listed above may occur in some people.

Do not be alarmed by this list of possible side effects.

You may not experience any of them.

After taking it

Storage

Keep LEXAPRO tablets in the blister pack until it is time to take them.

If you take the tablets out of the box or the blister pack they may not keep well.

Keep LEXAPRO tablets in a cool dry place where the temperature stays below 30°C.

Do not store it or any other medicine in the bathroom, near a sink, or on a window-sill.

Do not leave it in the car.

Heat and damp can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking LEXAPRO, or the medicine has passed its expiry date, ask your pharmacist what to do with any that is left over.

Return any unused medicine to your pharmacist.

Product description

What it looks like

LEXAPRO comes in two types of tablets:

- LEXAPRO 10 mg film-coated tablets - oval, white, scored and marked with "E" and "L" on each side of the score on one side of the tablet.
- LEXAPRO 20 mg film-coated tablets - oval, white, scored and marked with "E" and "N" on each side of the score on one side of the tablet.

A box contains 28 tablets.

Ingredients

Active ingredient(s):

- LEXAPRO 10 mg tablets – 10 mg escitalopram (as oxalate) per tablet
- LEXAPRO 20 mg tablets – 20 mg escitalopram (as oxalate) per tablet

Inactive ingredients:

- microcrystalline cellulose
- croscarmellose sodium
- hypromellose
- macrogol 400
- magnesium stearate
- colloidal anhydrous silica

- purified talc
- titanium dioxide

LEXAPRO does not contain lactose, gluten, sucrose, tartrazine or any other azo dyes.

Manufacturer/Sponsor

LEXAPRO is made by H. Lundbeck A/S, Denmark.

Distributed in Australia by:

Lundbeck Australia Pty Ltd
Ground Floor, 1 Innovation Road
North Ryde NSW 2113
Ph: +61 2 8669 1000

This leaflet was prepared on 25 August 2014.

Australian Registration Numbers:

LEXAPRO tablets

10 mg - AUST R 92051

20 mg - AUST R 92053

"Lexapro" is the registered trade mark of H. Lundbeck A/S.

AU- 661201-CMI

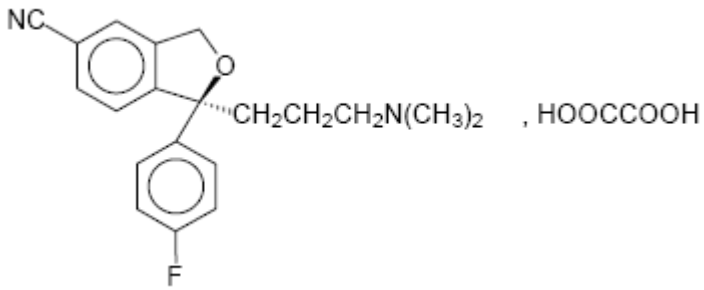
CHEMMART ESCITALOPRAM TABLETS

NAME OF THE MEDICINE

Escitalopram oxalate.

Chemical Name: *S*(+)-1-[3-(dimethylamino)propyl]-1-(4-flurophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrogen oxalate

Structural Formula:



Molecular Formula: $C_{20}H_{21}FN_2O.C_2H_2O_4$

Molecular Weight: 414.42

CAS Registry Number: 219861-08-2

DESCRIPTION

Escitalopram is the active enantiomer (*S*-enantiomer) of citalopram. Escitalopram oxalate is a fine white to yellow, crystalline material.

Escitalopram oxalate is sparingly soluble in water, slightly soluble in acetone, soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

Each tablet contains 10 or 20 mg escitalopram (as oxalate). In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, colloidal anhydrous silica, purified talc, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

PHARMACOLOGY

Pharmacological Actions

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT)-uptake (*in vitro* IC_{50} 2 nM).

The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.

Escitalopram is a highly selective Serotonin Reuptake Inhibitor (SSRI). On the basis of *in vitro* studies, escitalopram had no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRIs, escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and DA D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity.

Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter.

Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Escitalopram is the *S*-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the *R*-enantiomer is not inert but counteracts the serotonin-enhancing properties of the *S*-enantiomer in citalopram.

In healthy volunteers and in patients, escitalopram did not cause clinically significant changes in vital signs, ECGs or laboratory parameters.

S-demethylcitalopram, the main plasma metabolite, attains about 30% of parent compound levels after oral dosing and is about 5-fold less potent at inhibiting 5-HT reuptake than escitalopram *in vitro*. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 hours after multiple dosing). While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (about 80%).

Distribution

The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%.

Metabolism

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing, the mean concentrations of the demethyl and didemethyl metabolites are usually 28–31% and < 5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Excretion

The elimination half-life ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and renal routes with the major part of the dose excreted as metabolites in urine. Approximately 8.0% of escitalopram is eliminated unchanged in urine and 9.6% as the *S*-demethylcitalopram metabolite based on 20 mg escitalopram data. Hepatic clearance is mainly by the P450 enzyme system.

The pharmacokinetics of escitalopram are linear over the clinical dosage range. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (range 20 – 125 nmol/L) are achieved at a daily dose of 10 mg.

Hepatic Impairment

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

While there is no specific data, the use of escitalopram in reduced renal function may be extrapolated from that of racemic citalopram. Escitalopram is expected to be eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram

concentrations in serum, At present, no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Pharmacokinetics in Elderly Patients (> 65 years)

Escitalopram pharmacokinetics in subjects > 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients.

Gender

In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Polymorphism

It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

Escitalopram should not be used for the treatment of major depression and obsessive-compulsive disorder in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Major Depression

Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years.

Two fixed dose studies and one flexible dose study have shown escitalopram in the dose range 10–20 mg/day to be more efficacious than placebo in the treatment of depression. All three studies were randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. Two of the studies included an active reference (citalopram). All three studies consisted of a 1-week single-blind placebo lead-in period followed by an 8-week double-blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of 10 items that measure core symptoms of depression, such as sadness, tension, pessimism and suicidal thoughts. Each item is rated on a scale of 0 (no abnormality) to 6 (severe). The populations studied were therefore defined as suffering from moderate to severe depression (mean MADRS score 29). A total of 591 patients received escitalopram in these studies.

All three studies showed escitalopram to be statistically significantly superior to placebo on the ITT LOCF analysis of the mean change from baseline in the MADRS total score ($p \leq 0.01$). The magnitude of the difference between escitalopram and placebo in the MADRS change score ranged from 2.7 to 4.6 (mean of these values: 3.6). The magnitude of the difference for citalopram ranged from 1.5 to 2.5 (mean of these values: 2.0). The magnitude of the difference is larger with escitalopram than with citalopram.

Escitalopram demonstrated a significant early difference compared to placebo from week 2 onwards on the MADRS (week 1 in observed cases analysis). Likewise, the Clinical Global Impression-Improvement items (CGI-I) differed significantly from placebo from week 1 onwards. These early differences were not seen with racemic citalopram.

In the study with two parallel escitalopram dose groups, analysis of sub-groups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D > 25) receiving 20 mg/day as compared to 10 mg/day. The Hamilton Rating Scale for Depression (HAM-D) consists of 17 to 24 items reflecting core symptoms of depression. Each item is scored on a 3, 4 or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

In a fourth flexible-dose study with a similar design, the primary analysis did not distinguish a significant drug/placebo difference for either escitalopram or citalopram over 8 weeks on the MADRS change score in the LOCF dataset. However, on the basis of the OC analysis, both escitalopram and citalopram were significantly better than placebo ($p \leq 0.05$; difference between escitalopram and placebo: 2.9).

Escitalopram demonstrated efficacy in the treatment of anxiety symptoms associated with depression. In the three positive double-blind placebo-controlled studies, escitalopram was shown to be effective compared to placebo on the MADRS anxiety items; inner tension and sleep disturbances. Furthermore, in the one study where the Hamilton Anxiety Scale (HAM-A) and the anxiety factor of the Hamilton Depression Rating Scale (HAM-D scale) were used, results have shown that escitalopram was significantly better than placebo.

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open-label treatment phase with escitalopram 10 or 20 mg/day, were randomised to continuation of escitalopram at the same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined as a decrease of the MADRS total score to ≤ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22 or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo (26% vs. 40%; hazard ratio = 0.56, $p = 0.013$).

Further evidence of long-term efficacy is provided in a 6-month study which compared escitalopram 10 mg/day to citalopram 20 mg/day over a 6-month treatment period. Analysis of the primary end-point (the development of the MADRS total scores over 24 weeks) demonstrated escitalopram to be at least as efficacious as citalopram in the long-term treatment of depression. Secondary analyses showed that, while both treatments resulted in numerical improvements in ratings in the MADRS, HAM-A and the CGI, escitalopram was statistically superior to citalopram in several analyses, both during and at the end of the study.

Additional supportive evidence of the sustained efficacy of escitalopram treatment is demonstrated in an open-label 12-month study. The efficacy of escitalopram was maintained throughout the study, as measured by the MADRS total score and CGI-S score. Patients showed continued improvement, with total MADRS scores falling from 14.2 at baseline to 5.8 at last assessment and CGI-scores falling from 2.7 at baseline to 1.6 at last assessment.

A study in the elderly did not provide conclusive efficacy results for escitalopram, as the reference drug (fluoxetine) failed to differentiate from placebo. However, safety data from this study showed escitalopram to be well tolerated.

Obsessive-Compulsive Disorder (OCD)

Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years.

Efficacy of escitalopram in the treatment of OCD was investigated in two clinical trials, a 24-week placebo-controlled, fixed-dose study (with efficacy assessments at week 12 and week 24) and a 16 + 24-week placebo-controlled relapse-prevention study.

Patients included in these studies were male and female outpatients aged 18–65 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria and a pre-defined minimum score of 20 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients had actual baseline Y-BOCS scores of approx. 27, indicating significant OCD symptomatology. A structured clinical interview, the Mini International Neuropsychiatric Interview (MINI), was used to assist in the diagnosis and to exclude relevant psychiatric comorbidities. In order to avoid the confounding variable of significant concomitant depression, patients with more than mild depressive symptoms, i.e. a score of 22 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS), were excluded. To ensure a relatively homogenous population with OCD, patients currently diagnosed with any other psychiatric disorders as per Axis I of DSM-IV-TR or any clinically significant unstable medical illness were also excluded.

Results at week 12 of the 24-week placebo-controlled, fixed-dose study are shown in Tables 1 and 2. In the short-term (12 weeks), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score.

Table 1

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 12 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]
ESC10 to PBO	-1.97 [-3.97; 0.02]
ESC20 to PBO	-3.21* [-5.19; -1.23]

* p ≤ 0.01

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Furthermore, escitalopram 20 mg/day was significantly more efficacious than placebo on the Y-BOCS subscale of rituals at week 12. Both escitalopram 10 mg/day and escitalopram 20 mg/day were significantly more efficacious than placebo on the Y-BOCS subscale of obsessions as well as on the NIMH-OCS total score, CGI-I score and CGI-S score.

Table 2

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 12 (FAS, LOCF, ANCOVA) [95% CI]				
	Y-BOCS Obsessional Sub-score	Y-BOCS Compulsive Sub-score	NIMH-OCS Score	CGI-I Score	CGI-S Score
ESC10 to PBO	-1.15* [-2.20; -0.10]	-1.01 [-2.04; 0.01]	-1.01** [-1.70; -0.33]	-0.36* [-0.66;-0.06]	-0.41* [-0.72; -0.09]
ESC20 to PBO	-2.05*** [-3.10; -1.01]	-1.34** [-2.37; -0.32]	-1.40*** [-2.08; -0.72]	-0.53*** [-0.83; -0.23]	-0.64*** [-0.95; -0.33]

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Results after 24 weeks showed that both escitalopram 10 mg/day ($p < 0.05$) and escitalopram 20 mg/day ($p < 0.01$) were significantly more efficacious than placebo as measured by the primary outcome measure, the Y-BOCS total score, as well as on the secondary subscales of Y-BOCS (obsessions and rituals) and the NIMH-OCS score (escitalopram 10 mg/day ($p < 0.01$) and escitalopram 20 mg/day ($p < 0.001$)).

Table 3

Long-term (24 weeks) fixed-dose study	Mean Change from Baseline to Week 24 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]
ESC10 to PBO	-2.56* [-4.93; -0.20]
ESC20 to PBO	-3.55** [-5.90; -1.20]

ESC (10 or 20 mg) vs. PBO: * p ≤ 0.05; ** p ≤ 0.01

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

The beneficial efficacy of long-term treatment with escitalopram was also demonstrated by the analyses of responders and remitters in this study as shown in Tables 4 and 5.

Table 4

Long-term (24 weeks) fixed-dose study	Responders (CGI-I ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	38.9	38.1
ESC10	50	58**
ESC20	57.9**	56.1**

ESC (10 or 20 mg) vs. PBO: * p ≤ 0.05; ** p ≤ 0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 5

Long-term (24 weeks) fixed-dose study	Remitters (CGI-S ≤ 2) (LOCF) (%)	
	12 weeks	24 weeks
PBO	11.5	26.5
ESC10	24.1*	41.1*
ESC20	28.1**	38.6

ESC (10 or 20 mg) vs. PBO: * p ≤ 0.05; ** p ≤ 0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Maintenance of efficacy and prevention of relapse were investigated in the relapse-prevention study. This 24-week relapse-prevention study was preceded by a 16-week open-label period with patients initially receiving escitalopram 10 mg/day. In case of lack of efficacy (as judged by the investigator), the dose could be increased to a maximum of 20 mg/day. If dose-limiting adverse effects occurred, it was permissible to decrease the dose to 10 mg/day. Thus the dose of escitalopram was flexible at 10–20 mg/day from week 2 to 12. Subsequently, the dose was fixed at the dose received at the end of week 12 until week 16 to allow stabilisation of the patient on this dose. Responders to treatment were defined as patients with a decrease in Y-BOCS total score from baseline by ≥ 25% at week 16 and remitters were defined as Y-BOCS ≤ 10. See Table 6 for responder and remitter rates at the end of the 16-week open-label phase.

Table 6

Relapse-prevention study (16-week open-label, flexible-dose phase)	Responders (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF) (%)	Remitters (Y-BOCS ≤ 10) (APTS I, LOCF) (%)
ESC	74.4	34.0

ESC = escitalopram 10 & 20 mg

Responders at the end of the above 16-week open-label treatment phase (escitalopram 10 mg: 30 responders; escitalopram 20 mg: 133 responders) entered the 24-week randomised, double-blind placebo-controlled relapse-prevention phase. Both escitalopram 10 mg/day (p = 0.014) and 20 mg/day (p < 0.001) showed significantly fewer relapses as seen in Table 7.

Table 7

Relapse-prevention study (24-week double-blind phase)		n	Number of relapses	% relapsed
10 mg dose group	ESC10	30	3	10.00*
	PBO	20	7	35.00
20 mg dose group	ESC20	133	35	26.32**
	PBO	137	74	54.01
10-20 mg dose group	ESC	163	38	23.31**

Relapse-prevention study (24-week double-blind phase)		n	Number of relapses	% relapsed
	PBO	157	81	51.59

ESC (10 or 20 mg) vs. PBO: * p ≤ 0.05; ** p ≤ 0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; ESC = escitalopram 10 & 20 mg; PBO = placebo

INDICATIONS

- Treatment of major depression.
- Treatment of obsessive-compulsive disorder.

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in the tablets (see **DESCRIPTION**).

Monoamine Oxidase Inhibitors

Escitalopram should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. Similarly, at least 14 days should be allowed after stopping escitalopram before starting a MAOI or RIMA. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI (see **INTERACTIONS WITH OTHER MEDICINES).**

Pimozide

Concomitant use in patients taking pimozide is contraindicated (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms are present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 – 16 week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder

(16 trials), obsessive-compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families or caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as the emergence of suicidality and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for escitalopram should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia / Psychomotor Restlessness

The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Haemorrhage

Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). Escitalopram should therefore be used with caution in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Hyponatraemia

Probably due to inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia has been reported as a rare adverse reaction with the use of SSRIs. Especially elderly patients seem to be a risk group.

Seizures

The drug should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency (see **PRECAUTIONS**, **Pre-Clinical Safety**).

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Mania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

ECT (Electroconvulsive Therapy)

There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advised.

Effect on Ability to Drive and Use Machines

Escitalopram does not impair intellectual function and psychomotor performance. However, as with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

Discontinuation

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.

The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 – 3 months or more). It is therefore advised that escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see **DOSAGE AND ADMINISTRATION**).

Cardiac Disease

Escitalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, escitalopram causes a small decrease in heart rate. Consequently, caution should be observed when escitalopram is initiated in patients with pre-existing slow heart rate.

Hepatic Impairment

In subjects with hepatic impairment, clearance of escitalopram was decreased and plasma concentrations were increased. The dose of escitalopram in hepatically impaired patients should

therefore be reduced (see **PHARMACOLOGY, Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Escitalopram is extensively metabolised and excretion of unchanged drug in urine is a minor route of elimination. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) and escitalopram should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Pre-Clinical Safety

High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least 8-fold greater than anticipated clinically, have been associated with convulsions, ECG abnormalities and cardiovascular changes in experimental animals. Of the cardiovascular changes, cardiotoxicity (including congestive heart failure) was observed in comparative toxicological studies in rats following oral escitalopram or citalopram administration for 4 to 13 weeks and appears to correlate with peak plasma concentrations although its exact mechanism is not clear. Clinical experiences with citalopram and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Effects on Fertility

No fertility studies were performed with escitalopram. However, other non-clinical studies suggest that the effects of escitalopram can be directly predicted from those of citalopram racemate.

In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Animal data have shown that some SSRIs induce a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm. No animal data related to this aspect are available for escitalopram.

Animal data have shown that some SSRIs may affect sperm quality.

Use in Pregnancy (Category C)

Limited clinical data are available regarding exposure to escitalopram during pregnancy.

Newborns should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. If escitalopram is used until or shortly before birth, discontinuation effects in the newborn are possible. Abrupt discontinuation should be avoided during pregnancy.

Newborns exposed to escitalopram, other SSRIs (Selective Serotonin Reuptake Inhibitors) or SNRIs (Serotonin Norepinephrine Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In the majority of cases, the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological studies have shown that the use of SSRIs (including escitalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher than the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased post-implantation loss and reduced foetal weight at systemic exposure levels (based on AUC) ca. 11-fold that anticipated clinically, with no effects seen at 6-fold. No teratogenicity was evident in this study at relative systemic exposure levels of ca. 15 (based on AUC).

There were no peri/postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) ca. 2-fold that anticipated clinically. However, the number of stillbirths was increased and the size, weight and postnatal survival of offspring were decreased at a relative systemic exposure level ca. 5.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit.

Use in Lactation

It is expected that escitalopram, like citalopram, will be excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4–5.1% (below the notional 10% level of concern).

Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use of escitalopram in breast-feeding women, the decision to breast-feed should always be made as an individual risk/benefit analysis.

Paediatric Use

The efficacy and safety of escitalopram has not been established in children and adolescents less than 18 years of age. Consequently, escitalopram should not be used in children and adolescents less than 18 years of age.

Use in the Elderly (> 65 years)

Escitalopram AUC and half-life were increased in subjects ≥ 65 years of age compared to younger subjects in a single-dose and a multiple-dose pharmacokinetic study. The dose of escitalopram in elderly patients should therefore be reduced (see **DOSAGE AND ADMINISTRATION**).

Carcinogenicity

No carcinogenicity studies were performed with escitalopram. However, other non-clinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

Citalopram did not show any carcinogenic activity in long-term oral studies using mice and rats at doses up to 240 and 80 mg/kg/day, respectively.

Genotoxicity

No genotoxicity studies were performed with escitalopram. However, other non-clinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

INTERACTIONS WITH OTHER MEDICINES

MAOIs

Co-administration with MAO inhibitors may cause serotonin syndrome (see **CONTRAINDICATIONS**).

Serotonin syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (Hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with escitalopram should be discontinued if such events occur and supportive symptomatic treatment initiated.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently

throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction with citalopram noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see **CONTRAINDICATIONS**).

Serotonergic Drugs

Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, *Hypericum perforatum* (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and Tryptophan

There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Medicines Affecting the Central Nervous System

Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines Lowering the Seizure Threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold [e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol].

Hepatic Enzymes

Escitalopram has a low potential for clinically significant drug interactions. *In vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1 and 3A4, and a weak inhibitor of 2D6.

Effects of Other Drugs on Escitalopram *in vivo*

The pharmacokinetics of escitalopram was not changed by co-administration with ritonavir (CYP3A4 inhibitor). Furthermore, co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Co-administration of escitalopram with omeprazole (a CYP2C19 inhibitor) resulted in a moderate (approximately 50%) increase in plasma concentrations of escitalopram and a small but statistically significant increase (31%) in the terminal half-life of escitalopram (see also **DOSAGE AND ADMINISTRATION, Poor Metabolisers of CYP2C19**).

Co-administration of escitalopram with cimetidine (moderately potent general enzyme inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluoxetine, fluvoxamine, lansoprazole and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement (see also **DOSAGE AND ADMINISTRATION, Poor Metabolisers of CYP2C19**).

Effects of Escitalopram on Other Drugs *in vivo*

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure) or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine (a CYP2D6 substrate) resulted in a two-fold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with metoprolol (a CYP2D6 substrate) resulted in a two-fold increase in plasma levels of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with escitalopram.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

Medicines that Interfere with Haemostasis (NSAIDs, Aspirin, Warfarin, etc)

Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with escitalopram.

Alcohol

The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse reactions observed with escitalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually decrease in intensity and frequency with continued treatment and generally do not lead to a cessation of therapy. Data from short-term placebo-controlled studies are presented below. The safety data from the long-term studies showed a similar profile.

Treatment-Emergent Adverse Events with an Incidence of ≥ 1% in Placebo-Controlled Trials

Figures marked with * in below table indicate adverse reactions where incidence with escitalopram is statistically significantly different from placebo ($p < 0.05$).

SYSTEM ORGAN CLASS AND PREFERRED TERM	PLACEBO		ESCITALOPRAM	
	n	(%)	n	(%)
Patients Treated	1795		2632	
Patients with Treatment Emergent Adverse Event	1135	(63.2)	1891	(71.8)
GASTROINTESTINAL SYSTEM DISORDERS				
Nausea	151	(8.4)	481	(18.3)*
Diarrhoea	91	(5.1)	207	(7.9)*
Mouth Dry	74	(4.1)	152	(5.8)*
Constipation	42	(2.3)	71	(2.7)
Abdominal Pain	47	(2.6)	68	(2.6)
Vomiting	29	(1.6)	54	(2.1)
Dyspepsia	30	(1.7)	33	(1.3)
Flatulence	15	(0.8)	31	(1.2)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS				
Headache	305	(17.0)	506	(19.2)
Dizziness	64	(6.3)	147	(5.6)*
Paraesthesia	13	(0.7)	35	(1.3)
Migraine	17	(0.9)	23	(0.8)
Tremor	15	(0.8)	33	(1.3)
PSYCHIATRIC DISORDERS				
Insomnia	82	(4.6)	245	(9.3)*
Somnolence	62	(3.5)	217	(8.2)*
Anorexia	12	(0.7)	56	(2.1)*

SYSTEM ORGAN CLASS AND PREFERRED TERM	PLACEBO		ESCITALOPRAM	
	n	(%)	n	(%)
Libido decreased	21	(1.2)	102	(3.9)*
Anxiety	44	(2.5)	77	(2.9)
Appetite decreased	8	(0.5)	35	(1.3)*
Agitation	6	(0.3)	33	(1.3)*
Nervousness	13	(0.7)	25	(1.0)
Dreaming Abnormal	18	(1.0)	41	(1.6)
Impotence [gs]	4	(0.6)	22	(2.2)*
RESPIRATORY SYSTEM DISORDERS				
Upper Respiratory Tract Infection	91	(5.1)	96	(3.6)
Coughing	18	(1.1)	24	(0.9)
Rhinitis	81	(4.8)	146	(5.5)
Sinusitis	24	(1.3)	46	(1.7)
Pharyngitis	44	(2.5)	57	(2.2)
Yawning	3	(0.2)	58	(2.2)*
Bronchitis	31	(1.7)*	26	(0.9)
BODY AS A WHOLE – GENERAL DISORDERS				
Influenza-like Symptoms	65	(3.6)	87	(3.3)
Fatigue	62	(3.5)	230	(8.7)*
Back Pain	61	(3.4)	74	(2.8)
SKIN AND APPENDAGES DISORDERS				
Sweating increased	27	(1.5)	145	(5.5)*
MUSCULOSKELETAL SYSTEM DISORDERS				
Arthralgia	22	(1.2)	27	(1.0)
REPRODUCTIVE DISORDERS, FEMALE				
Anorgasmia [gs]	3	(0.3)	47	(2.9)
METABOLIC AND NUTRITIONAL DISORDERS				
Weight increase	20	(1.1)	45	(1.7)
REPRODUCTIVE DISORDERS, MALE				
Ejaculation disorder [gs]	3	(0.5)	48	(4.7)*
Ejaculation failure [gs]	1	(0.2)	27	(2.7)*
CARDIOVASCULAR DISORDERS				
Hypertension	24	(1.3)*	13	(0.5)
HEART RATE AND RHYTHM DISORDERS				
Palpitations	15	(0.8)	30	(1.1)
SECONDARY TERMS				
Inflicted injury (unintended injury)	22	(1.2)	23	(0.8)

* = Statistically significant difference escitalopram vs. placebo ($p < 0.05$).

[gs] = gender specific

Adverse Events in Relation to Dose

The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg escitalopram groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials. The overall incidence rates of adverse events in 10 mg escitalopram treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day escitalopram treated patients was greater (86%). Common adverse events that occurred in the 20 mg/day escitalopram group with an incidence approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group are shown below.

Incidence of common adverse events* in patients with major depression receiving placebo, 10 mg/day escitalopram or 20 mg/day escitalopram			
ADVERSE EVENT	**PLACEBO (n = 311)**	**10 mg/day Escitalopram (n = 310)**	**20 mg/day Escitalopram (n = 125)**
Insomnia	4%	7%	14%
Diarrhoea	5%	6%	14%
Dry mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating increased	< 1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

* adverse events with an incidence rate of at least 5% in either escitalopram group and with an incidence rate in 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group.

Vital Sign Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment.

ECG Changes

Cases of QT prolongation have been reported during the post-marketing period with both citalopram and escitalopram. Citalopram can cause dose-dependent QT interval prolongation. In an ECG study, the observed change from baseline QTc (Fridericia correction) was 7.5 msec at the 20mg/day dose and 16.7 msec at the 60mg/day dose of citalopram. The effect of escitalopram on the QT interval was similarly studied at doses of 10mg/day and 30mg/day. The change from baseline QTc (Fridericia correction) was 4.3 msec at the 10mg/day dose and 10.7 msec with the above recommended dose of 30mg/day. The QTc interval prolongation observed with 60mg citalopram exceeded that observed with 30mg escitalopram. It is probable that the *R*-enantiomer and its metabolites in racemic citalopram contribute to these effects.

Weight Changes

Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

In clinical studies, there were no signals of clinically important changes in either various serum chemistry, haematology and urinalysis parameters associated with escitalopram treatment compared to placebo or in the incidence of patients meeting the criteria for potentially clinically significant changes from baseline in these variables.

For abnormal laboratory changes registered as either *uncommon events* or *serious adverse events from ongoing trials* and observed during (but not necessarily caused by) treatment with escitalopram, please refer to “Other Events Observed During the Pre-Marketing Evaluation of Escitalopram”.

Other Events Observed During the Pre-Marketing Evaluation of Escitalopram

Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1% and serious adverse events from ongoing trials. All reported events are included except those already listed in the table or elsewhere in the **ADVERSE EFFECTS** section and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with escitalopram, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients.

Application Site Disorders

Uncommon: otitis externa, cellulitis.

Body as a Whole

Uncommon: allergy, aggravated allergy, allergic reactions, asthenia, carpal tunnel syndrome, chest pain, chest tightness, fever, hernia, leg pain, limb pain, neck pain, oedema, oedema of extremities, peripheral oedema, rigors, malaise, syncope, scar.

Cardiovascular Disorders, General

Uncommon: hypertension aggravated, hypotension, hypertension, abnormal ECG.

Central and Peripheral Nervous System Disorders

Uncommon: ataxia, dysaesthesia, disequilibrium, dysgeusia, dystonia, hyperkinesia, hyperreflexia, hypertonia, hypoaesthesia, leg cramps, lightheadedness, muscle contractions, nerve root lesion, neuralgia, neuropathy, paralysis, sedation, tetany, tics, twitching, vertigo.

Gastrointestinal System Disorders

Uncommon: abdominal cramp, abdominal discomfort, belching, bloating, change in bowel habit, colitis, colitis ulcerative, enteritis, epigastric discomfort, gastritis, gastroesophageal reflux, haemorrhoids, heartburn, increased stool frequency, irritable bowel syndrome, melaena, periodontal destruction, rectal haemorrhage, tooth disorder, toothache, ulcerative stomatitis.

Hearing and Vestibular Disorders

Uncommon: deafness, earache, ear disorder, otosalpingitis, tinnitus.

Heart Rate and Rhythm Disorders

Uncommon: bradycardia, tachycardia.

Liver and Biliary System Disorders

Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and Nutritional Disorders

Uncommon: abnormal glucose tolerance, diabetes mellitus, gout, hypercholesterolaemia, hyperglycaemia, hyperlipaemia, thirst, weight decrease, xerophthalmia.

Musculoskeletal System Disorders

Uncommon: arthritis, arthropathy, arthrosis, bursitis, costochondritis, fascitis plantar, fibromyalgia, ischial neuralgia, jaw stiffness, muscle cramp, muscle spasms, muscle stiffness, muscle tightness, muscle weakness, myalgia, myopathy, osteoporosis, pain neck/shoulder, tendinitis, tenosynovitis.

Myo-, Endo- and Pericardial and Valve Disorders

Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm

Uncommon: female breast neoplasm, ovarian cyst, uterine fibroid.

Platelet, Bleeding and Clotting Disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Poison Specific Terms

Uncommon: sting.

Psychiatric Disorders

Uncommon: aggressive reaction, amnesia, apathy, bruxism, carbohydrate craving, concentration impairment, confusion, depersonalisation, depression, depression aggravated, emotional lability, excitability, feeling unreal, forgetfulness, hallucination, hypomania, increased appetite, irritability, jitteriness, lethargy, loss of libido, obsessive-compulsive disorder, panic reaction, paroniria, restlessness aggravated, sleep disorder, snoring, suicide attempt, thinking abnormal.

Red Blood Cell Disorders

Uncommon: anaemia hypochromic, anaemia.

Reproductive Disorders / Female

Uncommon: amenorrhoea, atrophic vaginitis, breast pain, genital infection, intermenstrual bleeding, menopausal symptoms, menorrhagia, menstrual cramps, menstrual disorder, premenstrual tension, postmenopausal bleeding, sexual function abnormality, unintended pregnancy, dysmenorrhoea, vaginal haemorrhage, vaginal candidiasis, vaginitis.

Reproductive Disorders / Male

Uncommon: ejaculation delayed, prostatic disorder.

Resistance Mechanism Disorders

Uncommon: moniliasis genital, abscess, infection, herpes simplex, herpes zoster, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis.

Respiratory System Disorders

Uncommon: asthma, dyspnoea, laryngitis, nasal congestion, nasopharyngitis, pneumonia, respiratory tract infection, shortness of breath, sinus congestion, sinus headache, sleep apnoea, tracheitis, throat tightness.

Skin and Appendages Disorders

Uncommon: acne, alopecia, dermatitis, dermatitis fungal, dermatitis lichenoid, dry skin, eczema, erythematous rash, furunculosis, onychomycosis, pruritus, psoriasis aggravated, rash, rash pustular, skin disorder, urticaria, verruca.

Secondary Terms

Uncommon: accidental injury, bite, burn, fall, fractured neck of femur, alcohol problem, traumatic haematoma, cyst, food poisoning, lumbar disc lesion, surgical intervention.

Special Senses Other, Disorders

Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS, vision blurred.

Urinary System Disorders

Uncommon: cystitis, dysuria, facial oedema, micturition frequency, micturition disorder, nocturia, polyuria, pyelonephritis, renal calculus, urinary frequency, urinary incontinence, urinary tract infection.

Vascular (Extracardiac) Disorders

Uncommon: cerebrovascular disorder, flushing, hot flush [gs], ocular haemorrhage, peripheral ischaemia, varicose vein, vein disorder, vein distended.

Vision Disorders

Uncommon: accommodation abnormal, blepharospasm, eye infection, eye pain, mydriasis, vision abnormal, vision blurred, visual disturbance.

White Cell and Reticuloendothelial System Disorders

Uncommon: leucopenia.

In addition, the following adverse reactions have been reported with racemic citalopram (all of which have also been reported for other SSRIs):

Disorders of Metabolism and Nutrition:
Hyponatraemia, inappropriate ADH secretion (both especially in elderly women).

Neurological Disorders:
Convulsions, convulsions grand mal and extrapyramidal disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia and inco-ordination).

Skin Disorders:
Ecchymoses, angioedema.

Furthermore, a number of adverse reactions have been listed for other SSRIs. Although these are not listed as adverse reactions for escitalopram or citalopram, it cannot be excluded that these adverse reactions may occur with escitalopram. These SSRI class reactions are listed below:

Cardiovascular Disorders:	postural hypotension.
Hepatobiliary Disorders:	abnormal liver function tests.
Neurological Disorders:	movement disorders.
Psychiatric Disorders:	mania, panic attacks.
Renal and Urinary Disorders:	urinary retention.
Reproductive Disorders:	galactorrhoea.

Other Events Observed During the Post-Marketing Evaluation of Escitalopram

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported in association with escitalopram treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the **ADVERSE EFFECTS** section:

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental overdose, injury NOS, psychotic disorder.

In addition, although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment subsequent to the marketing of racemic citalopram and were not observed during the pre-marketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, anaphylaxis, choreoathetosis, delirium, dyskinesia, epidermal necrolysis, erythema multiforme, gastrointestinal haemorrhage, haemolytic anaemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinaemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia and withdrawal syndrome.

Class Effect

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

DOSAGE AND ADMINISTRATION

Adults

Escitalopram is administered as a single oral dose and may be taken with or without food.

Major Depression

The recommended dose is 10 mg (one 10 mg tablet) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet) daily.

Usually 2 – 4 weeks are necessary for antidepressant response, although the onset of therapeutic effect may be seen earlier. The treatment of a single episode of depression requires treatment over the acute and the medium term. After the symptoms resolve during acute treatment, a period of consolidation of the response is required. Therefore, treatment of a depressive episode should be continued for a minimum of 6 months.

Obsessive-Compulsive Disorder

The recommended starting dose is 10 mg (one 10 mg tablet) once daily. Depending on individual patient response, the dose may be increased to 20 mg (one 20 mg tablet) daily.

Long-term treatment has been studied for a maximum of 40 weeks. Patients responding to a 16-week open-label treatment phase were randomised to a 24-week placebo-controlled relapse-prevention phase, receiving 10 or 20 mg escitalopram daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly Patients (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg (one 10 mg tablet) is the recommended maximum maintenance dose in the elderly (see **PHARMACOLOGY, Pharmacokinetics** and **PRECAUTIONS**).

Paediatric Use

Safety and efficacy have not been established in this population. Escitalopram should not be used in children and adolescents under 18 years of age (see **PRECAUTIONS**).

Hepatic Impairment

An initial dose of 5 mg (half a 10 mg tablet) daily for the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet) (see **PRECAUTIONS**).

Renal Impairment

Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) (see **PRECAUTIONS**).

Poor Metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg (half a 10 mg tablet) daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet) (see **PHARMACOLOGY**, **Pharmacokinetics** and **PRECAUTIONS, Interactions with Other Medicines**).

Discontinuation

Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over a period of at least one to two weeks is recommended. If unacceptable discontinuation symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the dose may be decreased but at a more gradual rate.

OVERDOSAGE

In general, the main therapy for all overdoses is supportive and symptomatic care.

Toxicity

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases, mild or no symptoms have been reported. Doses between 400 and 800 mg of escitalopram alone have been taken without any severe symptoms. No fatalities or

sequelae were reported in the few cases with a higher dose (one patient survived ingestion of either 2,400 or 4,800 mg).

Symptoms

Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting), the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation) and electrolyte/fluid balance conditions.

Treatment

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Chemmart Escitalopram tablets are intended for oral administration.
Each tablet contains 10 mg or 20 mg escitalopram (as oxalate) as the active ingredient.

10 mg tablets: White to off -white, oval, biconvex, film-coated tablets with “C4” embossed on one side and have a notch break-line on the other side.
Blister pack (PVC/PVdC/Al) of 28 tablets – AUST R 213723.

20 mg tablets: White to off -white, oval, biconvex, film-coated tablets with “C3” embossed on one side and a notch break-line on the other side.
Blister pack (PVC/PVdC/Al) of 28 tablets – AUST R 213724.

* Not all strengths may be available.

Storage

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 11 July 2013

DATE OF MOST RECENT AMENDMENT: 03 December 2015

Chemmart Escitalopram

Contains the active ingredient, escitalopram (as escitalopram oxalate)

Consumer Medicine Information

For a copy of a large print leaflet, Ph: 1800 195 055

What is in this leaflet

Read this leaflet carefully before taking your medicine.

This leaflet answers some common questions about escitalopram.

It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the last page. More recent information on this medicine may be available.

Ask your doctor or pharmacist:

- if there is anything you do not understand in this leaflet,
- if you are worried about taking your medicine, or
- to obtain the most up-to-date information.

You can also download the most up to date leaflet from www.apotex.com.au.

All medicines have risks and benefits. Your doctor has weighed the risks of you using this medicine against the benefits they expect it will have for you.

Pharmaceutical companies cannot give you medical advice or an individual diagnosis.

Keep this leaflet with your medicine.

You may want to read it again.

What this medicine is used for

The name of your medicine is Chemmart Escitalopram. It contains the active ingredient, escitalopram (as escitalopram oxalate).

It is used to treat

- depression
- obsessive-compulsive disorder.

Ask your doctor if you have any questions about why this medicine has been prescribed for you. Your doctor may have prescribed this medicine for another reason.

This medicine is available only with a doctor's prescription.

How it works

Escitalopram belongs to a group of medicines called Selective Serotonin Reuptake Inhibitors (SSRIs). Escitalopram and other SSRIs are thought to help by increasing the amount of serotonin in your brain.

Depression is longer lasting or more severe than the "low moods" everyone has from time to time due to the stress of everyday life. It is thought to be caused by a chemical imbalance in parts of the brain. This imbalance affects your whole body and can cause emotional and physical symptoms such as feeling low in spirit, loss of interest in activities, being unable to enjoy life, poor appetite or overeating, disturbed sleep, often waking up early, loss of sex drive, lack of energy and feeling guilty over nothing.

Escitalopram corrects this chemical imbalance and may help relieve the symptoms of depression.

There is no evidence that escitalopram is addictive. However, if you suddenly stop taking it, you may get side effects.

Tell your doctor if you get any side effects after stopping escitalopram.

Use in children

Do not give this medicine to a child or adolescent.

There is no experience with its use in children and adolescents under 18 years of age.

Before you take this medicine

When you must not take it

Do not take this medicine if:

- You are taking the following other medicines:

- pimozide, used to treat disorders which affect the way you think, feel or act
- monoamine oxidase inhibitors (MAOIs), used to treat depression (phenelzine, tranylcypromine, moclobemide), Parkinson's Disease (selegiline) or infections (linezolid).

Do not take escitalopram until 14 days after stopping most MAOIs. The exception is the MAOI, moclobemide, where you may take escitalopram one whole day after finishing taking moclobemide. Similarly, do not take any MAOI until at least 14 days after stopping taking escitalopram.

Taking escitalopram with MAOIs may cause a serious reaction with signs such as a sudden increase in body temperature, very high blood pressure, rigid muscles, nausea/ vomiting and/or fits (convulsions). Your doctor will know when it is safe to start escitalopram after the MAOI has been stopped.

- The expiry date (EXP) printed on the pack has passed.
- The packaging is torn, shows signs of tampering or it does not look quite right.
- **You have had an allergic reaction to escitalopram, citalopram or any of the ingredients listed at the end of this leaflet.**

Symptoms of an allergic reaction may include cough, shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin; fainting or hayfever-like symptoms.

If you think you are having an allergic reaction do not take any more of the medicine and contact your doctor immediately or go to the Accident and Emergency department at the nearest hospital.

Before you start to take it

Before you start taking this medicine, tell your doctor if:

1. **You have allergies to:**

- any other medicines
- any other substances such as foods, preservatives, lactose or dyes.

2. **You have or have had any medical conditions, especially the following:**

- mania, hypomania, bipolar disorder or any other conditions which affect the way you think, feel or act
- epilepsy or convulsions, fits or seizures (you should avoid taking escitalopram if your epilepsy is not properly controlled; if it is properly controlled your doctor will wish to watch you carefully if you take escitalopram)
- heart problems
- liver problems
- kidney problems
- problems with blood clotting or abnormal bleeding, i.e. a tendency to bleed or bruise easily
- thoughts or actions relating to self-harm or suicide
- diabetes
- a decreased level of sodium in your blood
- restlessness and/or a need to move often (akathisia)

3. **You are currently pregnant or you plan to become pregnant.**

   There have been reports that babies exposed to certain antidepressants during the third trimester of pregnancy may develop complications after birth.

   Do not take this medicine whilst pregnant until you and your doctor have discussed the risks and benefits involved.

4. **You are currently breast-feeding or you plan to breast-feed.**

   It is not recommended that you breast-feed while taking this medicine because escitalopram passes into breast milk and may affect your baby.

   Do not take this medicine whilst breast-feeding until you and your doctor have discussed the risks and benefits involved.

5. **You are receiving electroconvulsive therapy (ECT).**
6. **You are planning to have, or have very recently had, surgery or an anaesthetic.**
7. **You are currently receiving or are planning to receive dental treatment.**
8. You are taking or are planning to take any other medicines

This includes vitamins and supplements that are available from your pharmacy, supermarket or health food shop.

Some combinations of medicines may increase the risk of serious side effects and are potentially life-threatening.

Therefore some medicines MUST NOT be taken with escitalopram. These include:

- monoamine oxidase inhibitors, such as moclobemide, phenelzine, tranylcypromine, selegiline and linezolid
- pimozide

(see also "When you must not take it").

Some other medicines may interact with escitalopram.

These include:

- tryptophan, contained in some multivitamin and herbal preparations
- sumatriptan, used to treat migraines
- tramadol, a strong pain killer
- sumatriptan and similar medicines used to treat migraines and cluster headaches
- St John's Wort (Hypericum perforatum), a herbal remedy
- other medicines used to treat depression, including SSRIs, imipramine, clomipramine, nortriptyline and desipramine
- lithium, used to treat mood swings and some types of depression

- any other medicines used to treat anxiety, obsessive-compulsive disorder or pre-menstrual dysphoric disorder.
- antipsychotics, medicines used to treat psychoses, schizophrenia and other conditions which affect the way you think, feel or act (e.g. risperidone, thioridazine and haloperidol)
- any other medicines affecting the chemicals in the brain
- prochlorperazine, used to prevent or treat severe nausea and vomiting
- bupropion, a medicine helping to treat nicotine dependence
- mefloquine, an anti-malaria medicine
- some heart or blood pressure medications, e.g. dipyridamole, flecainide, propafenone, metoprolol
- medicines known to prolong bleeding e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and anti-coagulants (such as warfarin and ticlopidine), which are used to prevent blood clots
- medicines used to treat reflux and ulcers, such as cimetidine, omeprazole, esomeprazole and lansoprazole
- imipramine and desipramine types of antidepressants.

If you are taking any of these you may need a different dose or you may need to take different medicines.

Other medicines not listed above may also interact with escitalopram.

How to take this medicine

Follow carefully all directions given to you by your doctor.

Their instructions may be different to the information in this leaflet.

How much to take

Your doctor will tell you how much of this medicine you should take. This will depend on your condition and whether you are taking any other medicines.

The standard dose for this medicine is 10 mg per day. Your doctor may increase your dose to 20 mg per day depending on how you respond to this medicine.

Elderly people may need smaller doses. The maximum dose for elderly people is 10 mg per day.

Patients with liver disease or with a lack of certain liver enzymes may receive a lower initial dose of 5 mg daily for the first two weeks. Your doctor may increase the dose to 10 mg daily.

Do not stop taking your medicine or change your dosage without first checking with your doctor.

How to take it

Swallow the tablets whole with a full glass of water.

Do not chew them.

When to take it

Take escitalopram as a single dose, either in the morning or in the evening.

Take this medicine at the same time each day.

Taking it at the same time each day will have the best effect and will also help you remember when to take it.

It does not matter if you take it before, with or after food.

How long to take it for

Continue taking your medicine for as long as your doctor tells you, even if it takes some time before you feel any improvement in your condition.

Make sure you have enough to last over weekends and holidays.

As with other medicines for the treatment of these conditions, it may take a few weeks before you feel any improvement.

Individuals will vary greatly in their response to escitalopram.

Your doctor will check your progress at regular intervals.

The length of treatment may vary for each individual, but is usually at least 6 months.

In some cases, your doctor may decide that longer treatment is necessary.

Occasionally the symptoms of depression or other psychiatric conditions may include thoughts of harming yourself or committing suicide. It is possible that these symptoms may continue or increase until the full anti-depressant effect of your medicine becomes apparent.

You or anyone close to you or caring for you should watch for these symptoms and tell your doctor immediately or go to the nearest hospital if you have any distressing thoughts or experiences during this initial period or at any other time.

Also contact your doctor if you experience any worsening of your depression or other symptoms at any time during your treatment.

Stopping Treatment

Do not stop taking this medicine even if you begin to feel better.

Your doctor may decide that you should continue to take it for some time, even when you have overcome your problem. For best effect, this medicine must be taken regularly.

The underlying illness may persist for a long time and if you stop your treatment too soon, your symptoms may return.

Do not stop taking this medicine suddenly.

If you suddenly stop taking your medicine, you may experience mild, but usually temporary, symptoms such as dizziness, pins and needles, electric shock sensations, sleeping problems (vivid dreams, nightmares,

inability to sleep), feeling anxious, restless or agitated, headaches, feeling sick (nausea), vomiting, sweating, tremor (shaking), feeling confused, feeling emotional or irritable, diarrhoea, visual disturbances, or fast or irregular heartbeats.

When you have completed your course of treatment, the dose of escitalopram is gradually reduced over a couple of weeks rather than stopped abruptly.

Your doctor will tell you how to reduce the dosage so that you help avoid getting side effects.

If you forget to take it

If you missed a dose and remember in less than 12 hours, take it straight away, and then go back to taking it as you would normally.

Otherwise, if you are more than 12 hours late, skip the dose you missed and take the next dose when you are meant to.

Do not take a double dose to make up for missed doses.

This may increase the chance of you experiencing side effects.

If you have trouble remembering to take your medicine, ask your pharmacist for some hints to help you remember.

If you take too much (overdose)

If you think that you or anyone else may have taken too much of this medicine, immediately telephone your doctor or the Poisons Information Centre (Tel: 13 11 26 in Australia) for advice. Alternatively go to the Accident and Emergency Department at your nearest hospital.

Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

If you take too much escitalopram, you may get symptoms of drowsiness, sleepiness, dizziness, high or low blood pressure, nausea (feeling sick), vomiting, agitation or tremor (shaking), fast or slow heart beat or change in heart rhythm, dilated pupils or, rarely, temporary paralysis or weakness of muscles, convulsions or coma.

A condition called serotonin syndrome may occur, with high fever, agitation, confusion, trembling and abrupt contraction of muscles.

While you are taking this medicine

Things you must do

People taking escitalopram may be more likely to think about killing themselves or actually trying to do so, especially when escitalopram is first started or the dose is changed. Tell your doctor immediately if you have thoughts about killing yourself or if you are close to or care for someone using escitalopram who talks about or shows signs of killing him or herself.

All mentions of suicide or violence must be taken seriously.

Occasionally, the symptoms of depression may include thoughts of suicide or self-harm. It is possible that these symptoms continue or get worse until the full antidepressant effect of the medicine becomes apparent. This is more likely to occur if you are a young adult, i.e. 18 to 24 years of age, and you have not used antidepressant medicines before.

If you or someone you know or care for demonstrates any of the following warning signs of suicide-related behaviour while taking escitalopram, contact a doctor immediately, or even to go to the nearest hospital for treatment:

- thoughts or talk of death or suicide
- thoughts or talk of self-harm or harm to others
- any recent attempts of self-harm
- increase in aggressive behaviour, irritability or agitation
- worsening of depression.

Follow your doctor's instructions. Do not stop taking this medicine or change the dose without consulting your doctor, even if you experience increased anxiety at the beginning of treatment.

At the beginning of treatment, some patients may experience increased anxiety, which will disappear during continued treatment.

Tell your doctor immediately if you experience symptoms such as restlessness or difficulty sitting or standing still.

These symptoms can also occur during the first weeks of treatment.

Contact your doctor as soon as possible if you suddenly experience an episode of mania.

Some people with bipolar disorder (manic depression) may enter into a manic phase. Symptoms of mania include lots of rapidly changing thoughts or ideas, exaggerated gaiety, being much more physically active and much more restless.

Sometimes you may not know that you are manic, so it may be helpful to have a friend or relative watch over you for any possible signs of change in your behaviour.

Visit your doctor regularly so they can check on your progress.

Tell your doctor immediately if you become pregnant. If you are a woman of child-bearing age, you should avoid becoming pregnant while taking escitalopram.

Make sure your midwife and/or doctor know you are taking escitalopram. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like escitalopram may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after

the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

Low Sodium

Some people (especially older people or those taking diuretics/water tablets) may experience a lack of sodium in the blood when taking this medicine. Tell your doctor if you get a headache or start to feel sick, restless, irritated, confused or fatigued or if you vomit or have fits, muscle weakness or spasms.

Tell your doctor that you are taking this medicine if:

- you are about to be started on any new medicine
- you are breast-feeding or are planning to breastfeed
- you are about to have any blood tests
- you are going to have surgery or an anaesthetic or are going into hospital.

Your doctor may occasionally do tests to make sure the medicine is working and to prevent side effects.

Go to your doctor regularly for a check-up.

Tell any other doctors, dentists and pharmacists who are treating you that you take this medicine.

Tell your doctor if, for any reason, you have not taken your medicine exactly as prescribed.

Otherwise your doctor may think that it was not effective and change your treatment unnecessarily.

Tell your doctor if you feel this medicine is not helping your condition.

If you are being treated for depression, be sure to discuss with your doctor any problems you may have and how you feel, especially any feelings of severe sadness, thoughts of suicide, bursts of unusual energy, anger or aggression, or if you become particularly agitated or restless.

Tell your doctor immediately if you have any suicidal thoughts or other mental/mood changes.

Make sure you have enough tablets to last over weekends and holidays.

Things you must not do

Do not:

- Give this medicine to anyone else, even if their symptoms seem similar to yours.
- Take your medicine to treat any other condition unless your doctor or pharmacist tells you to.
- Stop taking your medicine, or change the dosage, without first checking with your doctor.

Do not let yourself run out of medicine over the weekend or on holidays.

Suddenly stopping escitalopram may cause unwanted discontinuation symptoms, such as dizziness, headache and nausea. Your doctor will tell you when and how escitalopram should be discontinued. You doctor will gradually reduce the amount you are using, usually over a period of one to two weeks, before stopping completely.

Things to be careful of

Be careful when driving or operating machinery until you know how this medicine affects you.

This medicine may cause nausea, fatigue, drowsiness, sight problems or dizziness in some people, especially early in the treatment. If you have any of these symptoms, do not drive, operate machinery, or do anything else that could be dangerous.

Avoid alcohol while you are taking this medicine.

It is best not to drink alcohol while you are being treated for depression.

You should be aware that people over 50 years of age who take antidepressants have an increased risk of having a bone fracture.

Possible side effects

Tell your doctor as soon as possible if you do not feel well while you are taking escitalopram or if you have any questions or concerns.

Do not be alarmed by the following lists of side effects. You may not experience any of them. All medicines can have side effects. Sometimes they are serious, but most of the time, they are not.

Tell your doctor if you notice any of the following:

- feeling tired and weak (fatigued), hot flushes, fever, feeling unwell, shaking or tremors, migraine, headache, or giddiness
- muscle, back, bone, nerve or joint pain, stiffness, weakness or cramps, decrease or loss of touch or other senses
- increased or decreased sensitivity to outside stimuli
- feeling or being sick, reflux, diarrhoea or loose bowel motions, constipation, indigestion, stomach pain or discomfort, wind, burping, hiccups, problems swallowing, sore mouth, tongue or throat, haemorrhoids (piles)
- dry mouth, feeling thirsty increased saliva, taste disturbance
- fatigue, sleepiness or drowsiness, yawning, ,sleeping difficulties, strange or terrifying dreams
- teeth grinding or clenching
- increased or decreased appetite, weight loss
- excessive and/or abnormal movements
- increased muscle tension, muscle twitching
- sexual problems, painful erection, prostate problems
- symptoms of hyperglycaemia (high blood sugar): feeling hungry, thirsty and/or frequent or excessive urination;
- problems with eyes or eyesight

- dizziness when you stand up suddenly, due to low blood pressure
- unable to tolerate alcohol
- menstrual irregularities, period pain, breast pain, unusual vaginal bleeding
- loss of bladder control unusual hair loss or thinning
- tingling or numbness of the hands or feet
- breast enlargement or unusual secretion of breast milk in men or women
- mild rash, or itching or prickling of the skin
- acne, eczema, dermatitis, dry skin, psoriasis or other skin problem
- pain of any type
- ringing or other persistent noise in the ears, problems hearing or earache
- increased or decreased sweating
- bruises
- osteoporosis
- tooth or jaw problems
- flu-like symptoms, runny or blocked nose, sneezing , facial pressure or pain, coughing or sore throat

Tell your doctor as soon as possible if you notice any of the following.

These may be serious side effects. You may need medical attention.

- becoming nervous, confused, forgetful, unable to concentrate, agitated, confused, panicky or anxious
- feeling restless or unable to sit still
- stomach pain with nausea and vomiting of blood, or blood in the bowel movements
- aggression, worsening of depression
- general swelling or swollen hands, ankles, feet or face or eye area due to fluid build-up
- problems speaking
- feelings of not being part of your body, or in a daze
- feeling sick or unwell with weak muscles or feeling confused (these symptoms may be signs of a rare condition as a result of low levels of sodium in the blood, which may be caused by antidepressants and occurs especially in elderly women)increased tendency to bleed, develop bruises or broken bones
- passing more or less urine than normal, or problems when urinating, or bladder infection
- abnormal liver function tests (increased amount of liver enzymes)
- flushing, varicose veins
- infection in any part of your body
- dizziness
- agitation, anxiety, feeling tense and restless, tired, drowsy, lack of energy, irritable, problems sleeping, headache, nausea and tingling or numbness of the hands and feet after stopping escitalopram.

If you experience any of the following, stop taking your medicine and contact your doctor immediately or go to the Accident and Emergency department at your nearest hospital.

These are very serious side effects. You may need urgent medical attention or hospitalisation.

- seizures, tremors, movement disorders (involuntary movements of the muscles or being unco-ordinated).
- coma (unconsciousness)
- a collection of symptoms including weight gain (despite loss of appetite), feeling and being sick, muscle weakness and irritability
- severe rash, with blisters and/ or excessive peeling of skin and also possibly severe blisters and bleeding in the lips, eyes, mouth, nose and genitals
- a sudden increase in body temperature, very high blood pressure, rigid muscles, nausea/ vomiting and/or fits (convulsions). These symptoms may be signs of a rare condition called Serotonin Syndrome.
- Neuroleptic Malignant Syndrome (a serious reaction to some medicines with a sudden increase in body temperature, extremely high blood pressure and severe convulsions)
- fast, slow or irregular heartbeat, high blood pressure
- palpitations, fainting or chest pain or tightness
- abnormal bleeding
- kidney pain, difficulty in passing urine, dark coloured urine or blood in the urine
- a collection of symptoms including fever, sore throat, swollen glands, mouth ulcers, unusual bleeding or bruising under the skin
- mania (mood of excitement, over-activity and uninhibited behaviour or aggression), hallucinations (hearing, seeing or feeling things that are not there)
- jaundice (yellowing of the skin and/or eyes) , with or without other signs of hepatitis or liver problems (loss of appetite, tiredness, feeling or being sick, dark urine, stomach pain or swelling, confusion, unconsciousness).
- feeling paranoid, panicky, or "high" or having mood swings or feeling more depressed or in a trance
- thoughts of suicide or attempting suicide or self-harm
- sudden, severe breathing problems
- sudden weakness or numbness of the face, arms or legs, especially on one side, slurred speech

Other side effects not listed above may also occur in some people.

Allergic reactions

If you think you are having an allergic reaction to escitalopram, do not take any more of this medicine and tell your doctor immediately or go to the Accident and Emergency department at your nearest hospital.

Symptoms of an allergic reaction may include some or all of the following:

- cough, shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue, throat or other parts of the body
- rash, itching or hives on the skin
- fainting
- hayfever-like symptoms

Storage and disposal

Storage

Keep your medicine in its original packaging until it is time to take it.

If you take your medicine out of its original packaging, it may not keep well.

Keep your medicine in a cool dry place where the temperature will stay below 30°C.

Do not store your medicine, or any other medicine, in the bathroom, or near a sink.

Do not leave it on a window-sill or in the car. Heat and dampness can destroy some medicines.

Keep this medicine where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine, or it has passed its expiry date, your pharmacist can dispose of the remaining medicine safely.

Product description

What Chemmart Escitalopram looks like

Chemmart Escitalopram tablets are available in the following strengths:

- 10 mg tablets: white to off - white, oval, biconvex, film-coated tablets with "C4" embossed on one side and a notch break-line on the other side.
- 20 mg tablets: white to off - white, oval, biconvex, film-coated tablets with "C3" embossed on one side and a notch break-line on the other side.

Blister packs of 28 tablets.

* Not all strengths may be available.

Ingredients

Each tablet contains 10 mg, or 20 mg of escitalopram (as oxalate) as the active ingredient.

It also contains the following inactive ingredients:

- microcrystalline cellulose
- colloidal anhydrous silica
- hypromellose
- magnesium stearate
- croscarmellose sodium
- purified talc
- macrogol 400
- titanium dioxide.

This medicine is gluten-free, lactose free, sucrose-free, tartrazine-free and free of other azo dyes.

Australian Registration Numbers

Chemmart Escitalopram 10 mg tablets (blister pack): AUST R 213723.

Chemmart Escitalopram 20 mg tablets (blister pack): AUST R 213724.

Sponsor

Apotex Pty Ltd

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